NORTHERA (droxidopa)
for the treatment of symptomatic neurogenic orthostatic hypotension

Food and Drug Administration NDA #203202

Cardiovascular and Renal Drugs Advisory Committee
14 January 2014

Chelsea Therapeutics, Inc.
Charlotte, NC

CHELSEA THERAPEUTICS

Agenda

Introduction	**William D. Schwieterman, MD** *Chief Medical Officer* *Chelsea Therapeutics*
Unmet Medical Need	**Roy Freeman, MD** *Professor of Neurology* *Harvard Medical School* *Director, Center for Autonomic and Peripheral Nerve Disorders* *Beth Israel Deaconess Medical Center*
Efficacy and Safety Results	**William D. Schwieterman, MD** *Chief Medical Officer* *Chelsea Therapeutics*
Cardiovascular Safety; **Overall Benefit/ Risk**	**William B. White, MD** *Professor of Medicine and Chief* *Division of Hypertension and Clinical Pharmacology; Cardiology Center* *University of Connecticut Health Center*

Invited External Experts

Expert	Affiliations	Field of Expertise
Brent A. Blumenstein, PhD	Statistical Consultant Trial Architecture Consulting	Biostatistics
Stewart A. Factor, DO	Professor of Neurology Director of Movement Disorders Program Emory University	Neurology
Horacio C. Kaufmann, MD	Professor of Neurology and Medicine Axelrod Professor of Dysautonomia Research New York University School of Medicine	Neurology
Gary G. Koch, PhD	Professor of Biostatistics University of North Carolina at Chapel Hill	Biostatistics
Stan Woollen	Senior Compliance Advisor Stan Woollen and Associates	GCP Compliance/ Quality Assurance

Proposed Indication

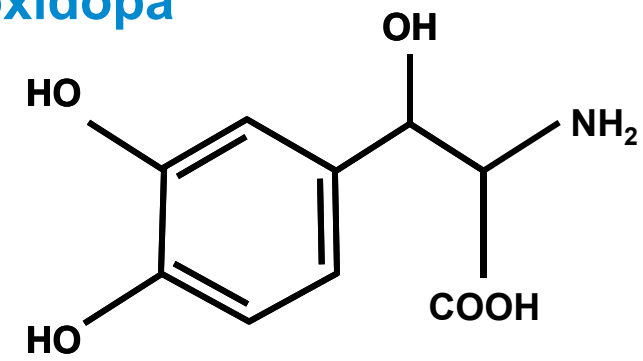
NORTHERA™ is indicated for the treatment of symptomatic neurogenic orthostatic hypotension (nOH) in adult patients with primary autonomic failure [Parkinson's Disease (PD), Multiple System Atrophy (MSA) and Pure Autonomic Failure (PAF)], Dopamine Beta Hydroxylase (DBH) Deficiency, and Non-Diabetic Autonomic Neuropathy (NDAN).

Proposed Dosing and Administration

- Dosage and administration (orally)
  - Initial dose: 100 mg TID
  - Dose increase: 100 mg TID increments
  - Maximum dose: 600 mg TID
- Dose optimization:
  - Based on patient's symptomatic response
  - Regular monitoring of supine BP
  - Reduce/stop if supine BP increases excessively
  - Last dose 3-4 hours before bedtime
- Dosage form and strengths
  - 100 mg, 200 mg, and 300 mg capsules

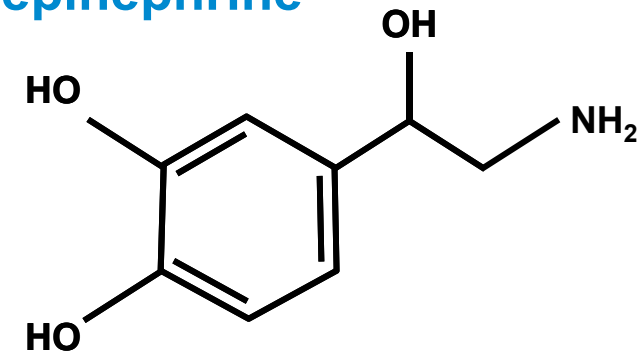
Droxidopa:
Prodrug of Norepinephrine

Droxidopa



Dopa Decarboxylase (DDC)

Norepinephrine



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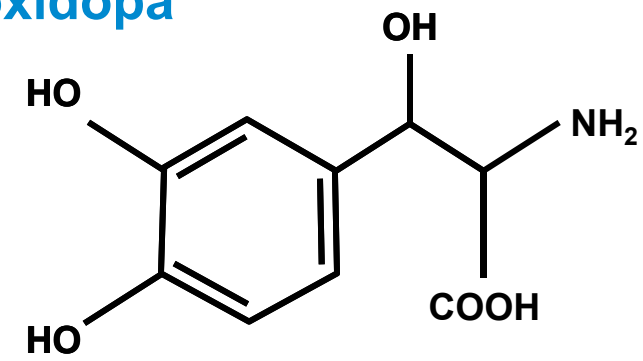
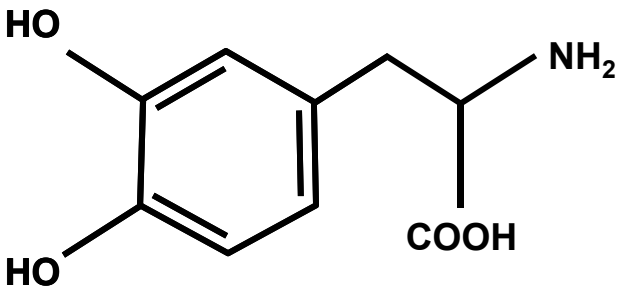


Levodopa



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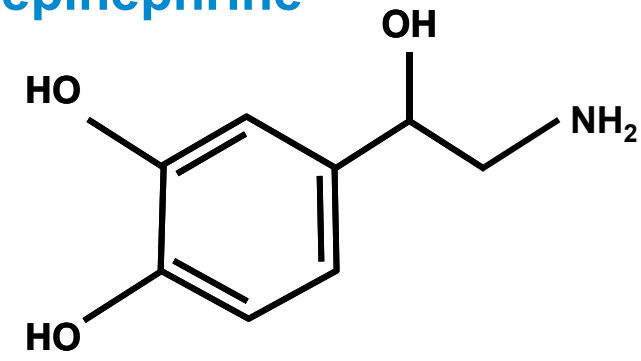
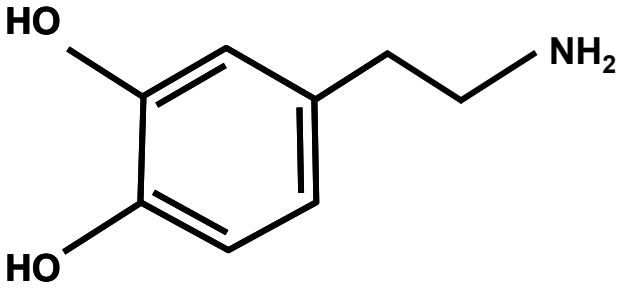
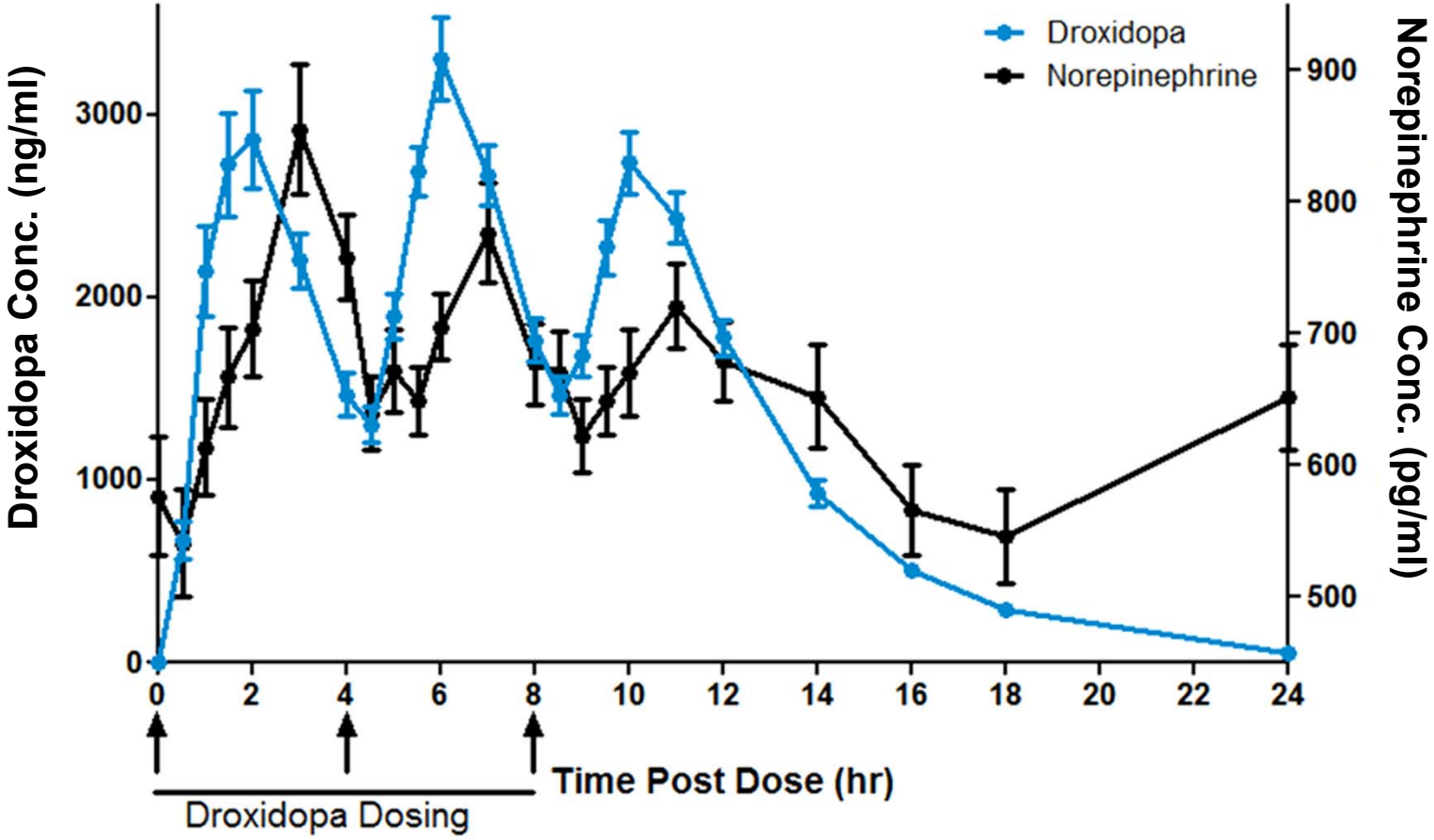


Dopamine



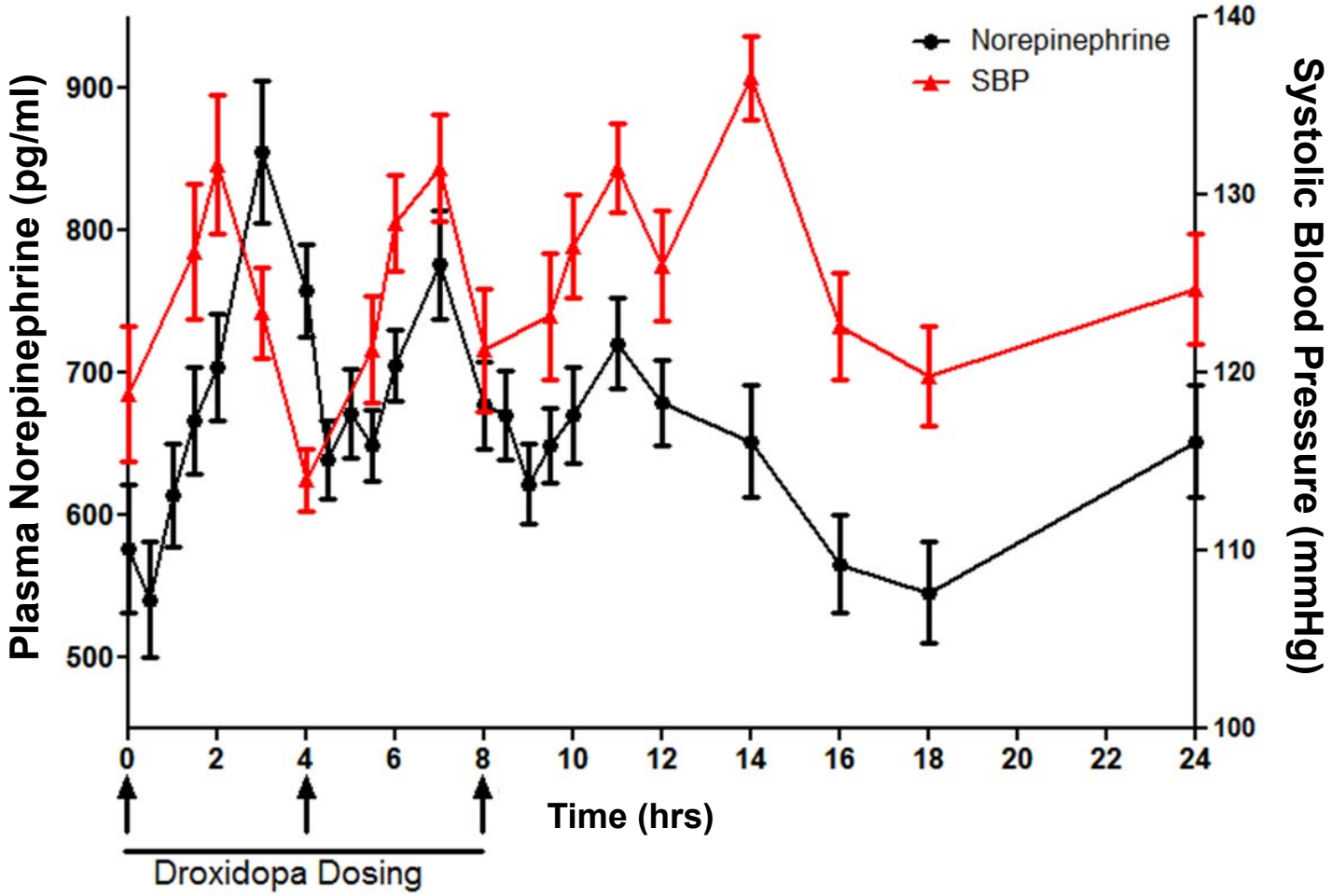
Mechanism of Action (Study 101)
Increases Plasma Norepinephrine

Droxidopa (3 x 100mg) Administered to Healthy Subjects at 4-hour Intervals

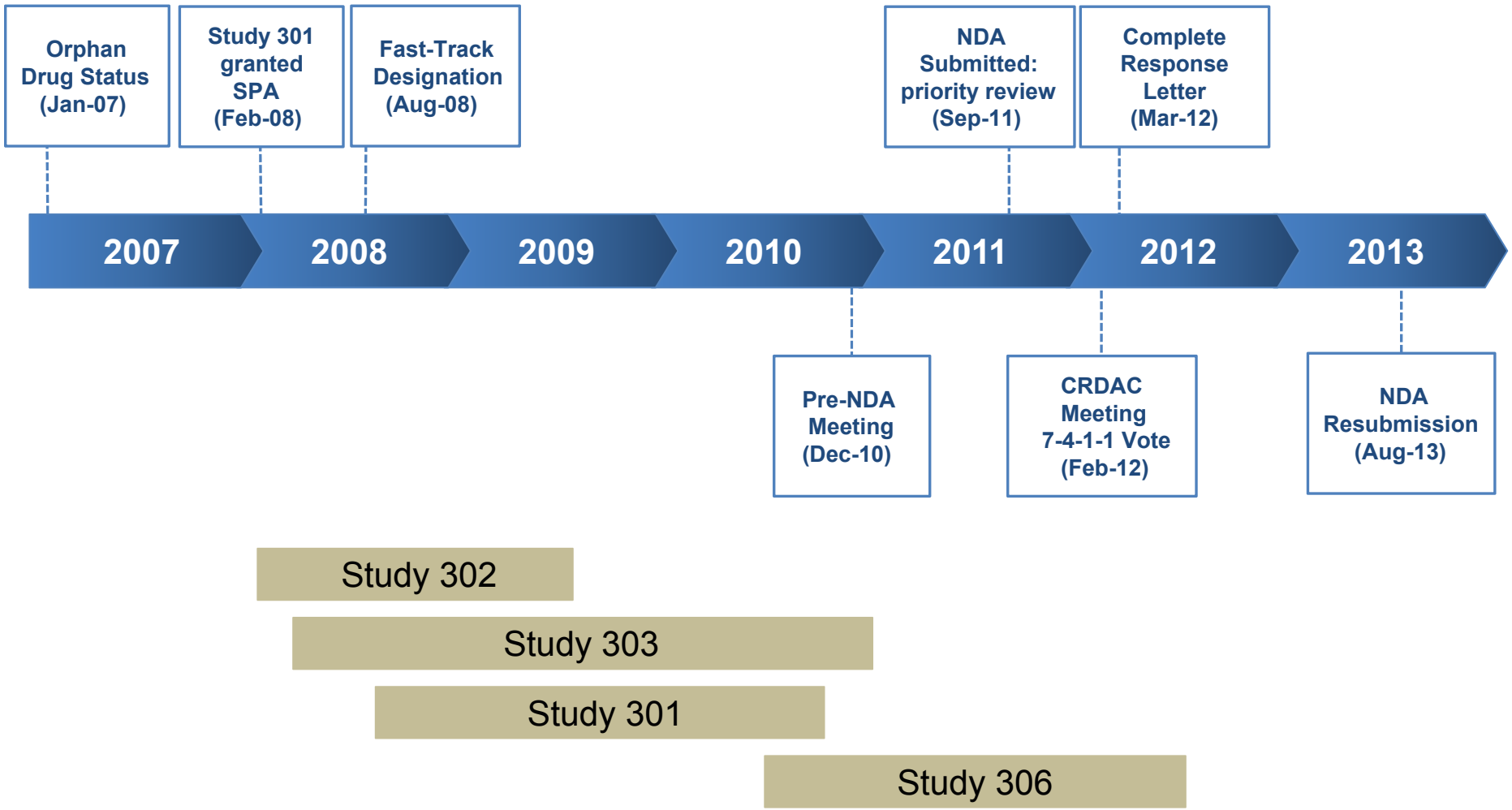


Mechanism of Action (Study 101)
Increases Blood Pressure

Droxidopa (3 x 100mg) Administered to Healthy Subjects at 4-hour Intervals



Key Regulatory Milestones



Regulatory Guidance

- FDA agrees Study 306B has the potential to serve as 2nd positive study (Jan 2013)
- FDA agrees short-term efficacy endpoints may be acceptable for approval and that durability potentially could be studied post-marketing (Jan 2013)
- FDA identifies two potential paths for approval (Mar 2013)

> *"…the Agency could consider full approval for treatment up to 1 week, as well as accelerated approval with a 1-week treatment effect serving as a surrogate for a longer-term effect"*
>
> FDA Correspondence; 20 March 2013

Commitment to Establishing Durability

Study 401

- Randomized, placebo-controlled, induction study
  - Target enrollment: 450 patients
  - Target completion: ~3 years
- Objectives
  - Evaluate dizziness over a 12 week treatment period
  - Evaluate reduction in patient-reported falls and fall-related injuries over a 12 week treatment period

Key Points:
Substantial Unmet Need Exists For nOH

- Symptomatic nOH is a serious, disabling orphan disorder
  - Limited safe and effective therapeutic options
  - Inherently difficult condition to study

Key Points:
Totality of Evidence Demonstrates Efficacy

- Symptomatic nOH is a serious, disabling orphan disorder
  - Limited safe and effective therapeutic options
  - Inherently difficult condition to study
- Two studies provide conclusive evidence that droxidopa provides short-term symptomatic benefits
  - Study 301: strong evidence of efficacy
  - Study 306B: confirms results from Study 301

Key Points:
Multiple Supportive Studies

- Symptomatic nOH is a serious, disabling orphan disorder
  - Limited safe and effective therapeutic options
  - Inherently difficult condition to study
- Two studies provide conclusive evidence that droxidopa provides short-term symptomatic benefits
  - Study 301: strong evidence of efficacy
  - Study 306B: confirms results from Study 301
- Study 302, Study 303, and multiple smaller studies
  - Support short-term efficacy
  - Suggest durability of effect
  - Demonstrate increases in standing SBP

Key Points:
Expanded Safety Database

- Expanded safety database
  - 10-week placebo-controlled comparative data
  - Comparative data during dose titration
- Droxidopa is safe and well tolerated

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Neurogenic Orthostatic Hypotension (nOH)

- Definition and causes
- Serious and disabling symptoms
- Unmet medical need
- Challenges in clinical trials

Definition of nOH

- A fall in blood pressure on standing
- Symptoms of cerebral hypoperfusion
- Dysfunction of the sympathetic nervous system - autonomic failure

Freeman R et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Autonomic Neuroscience – Basic and Clinical* 2011;161:46-8.

Definition of nOH

- A fall in blood pressure on standing
- Symptoms of cerebral hypoperfusion
- Dysfunction of the sympathetic nervous system - autonomic failure
- This is in contrast to OH due to:
  - Volume depletion
  - Dehydration
  - Vasodilatation

  - *More common*
  - *Different patient population*
  - *Sympathetic nervous system is <u>normal</u>*

Causes of nOH

- Occurs in:
  - Peripheral autonomic neuropathies
  - Pure autonomic failure
  - Dopamine β-hydroxylase (DBH) deficiency

  Only autonomic neurons

  - Multiple system atrophy (Shy Drager syndrome)
  - Parkinson disease with nOH

  Autonomic & motor neurons

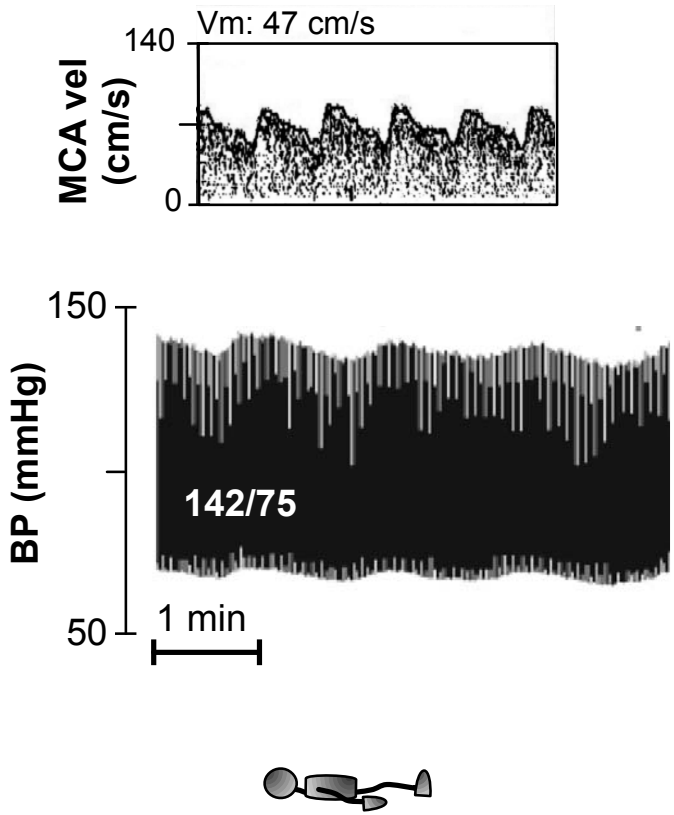
- The shared feature of these disorders is the failure to release NE appropriately on standing

Symptomatic nOH is an Orphan Condition

- Primary Autonomic Failure (~80,000 Patients)
  - Parkinson's Disease (PD) with nOH
  - Multiple System Atrophy (MSA)
  - Pure Autonomic Failure (PAF)
- Dopamine-β-Hydroxylase (DBH) Deficiency
- Non-Diabetic Autonomic Neuropathy (NDAN)

Hemodynamic Features of nOH:
52 year old patient with Multiple System Atrophy (MSA)

Cerebral blood flow velocity (Transcranial Doppler)



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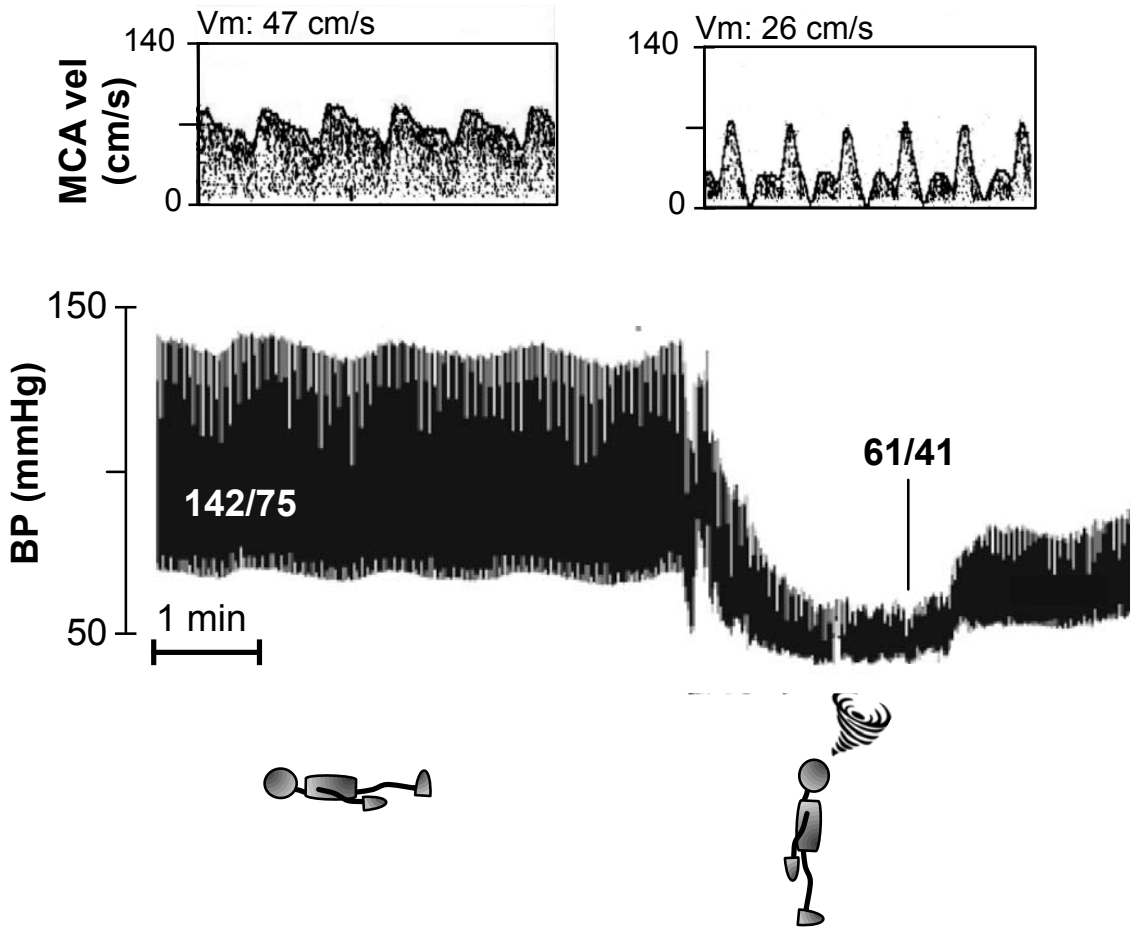

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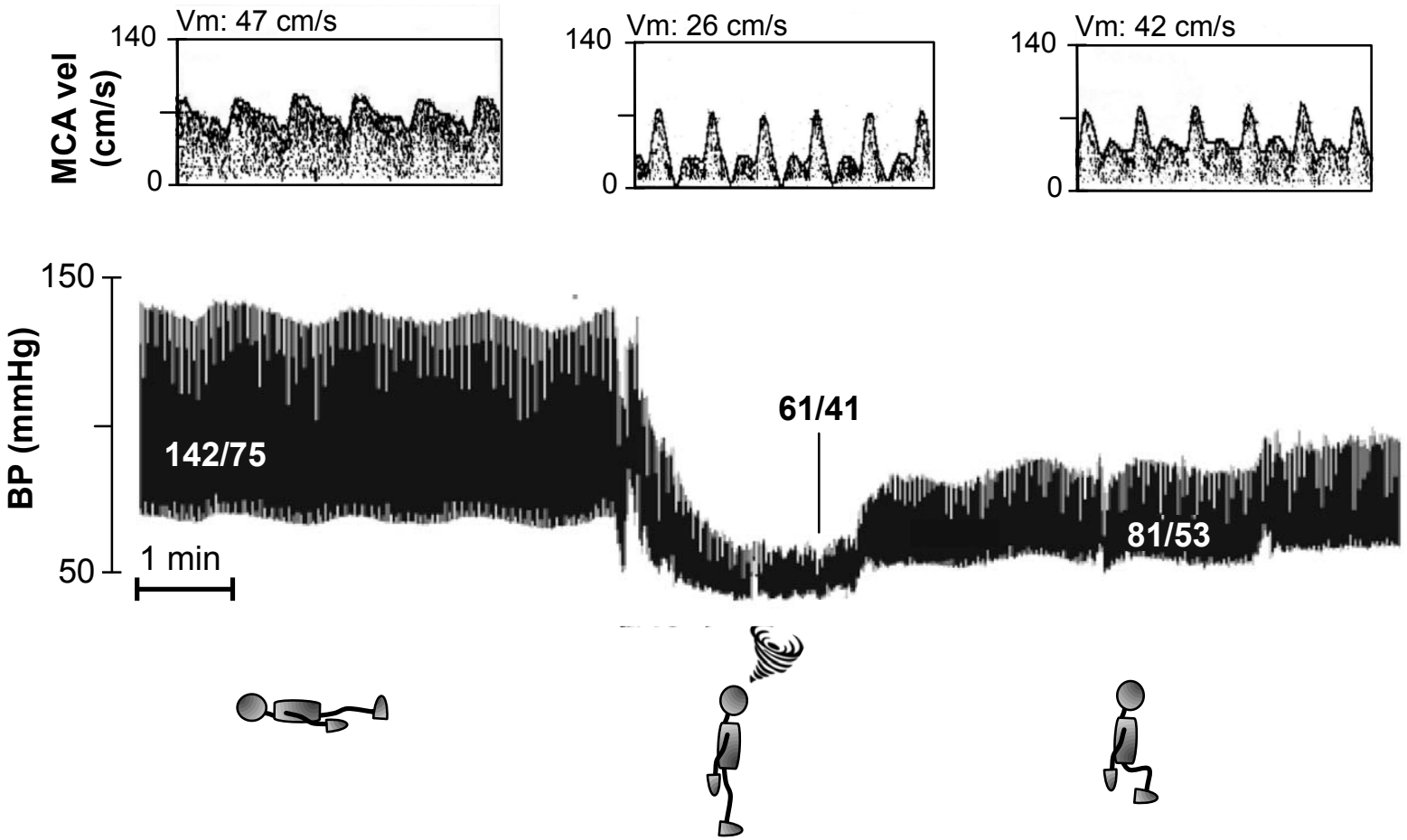
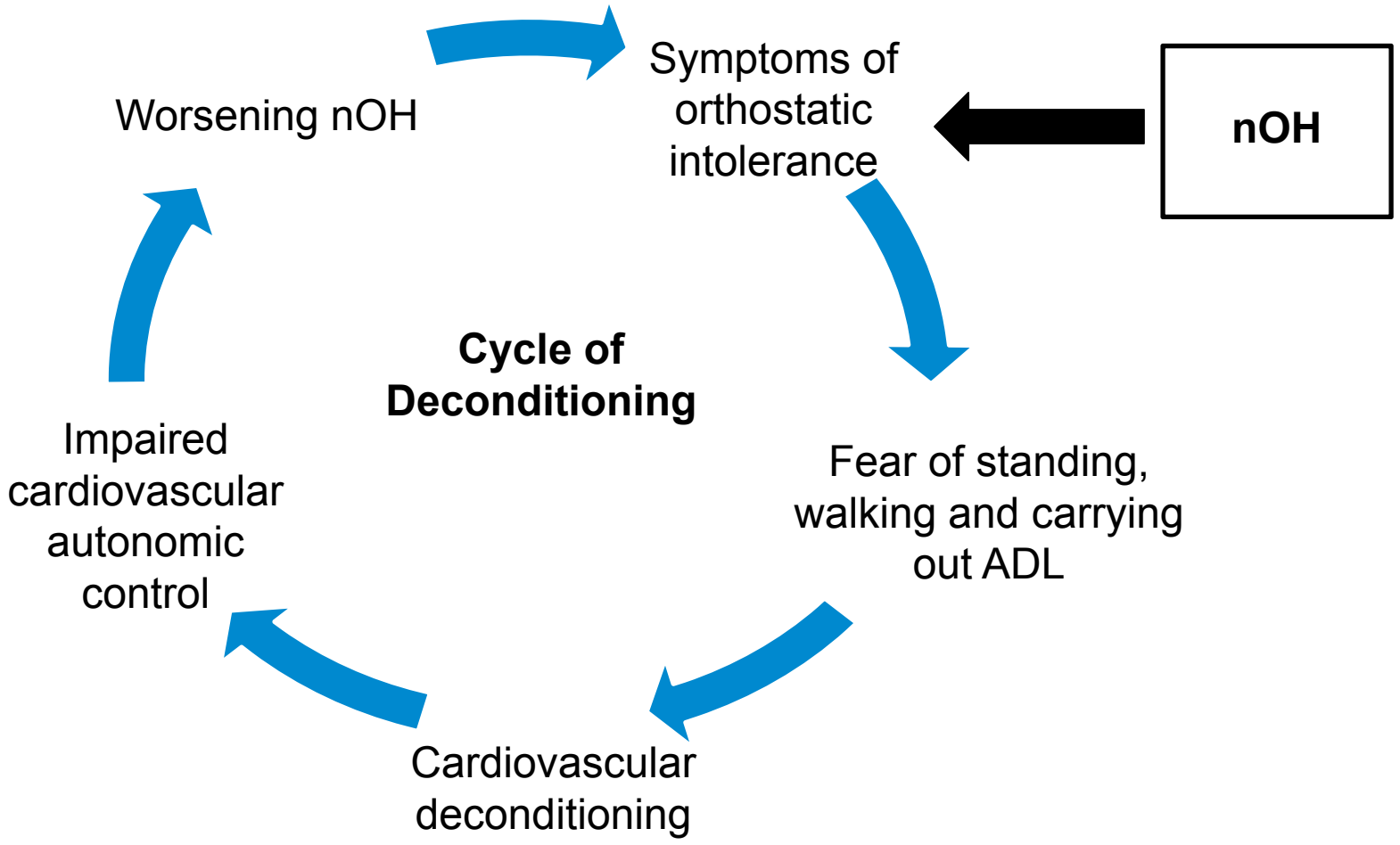
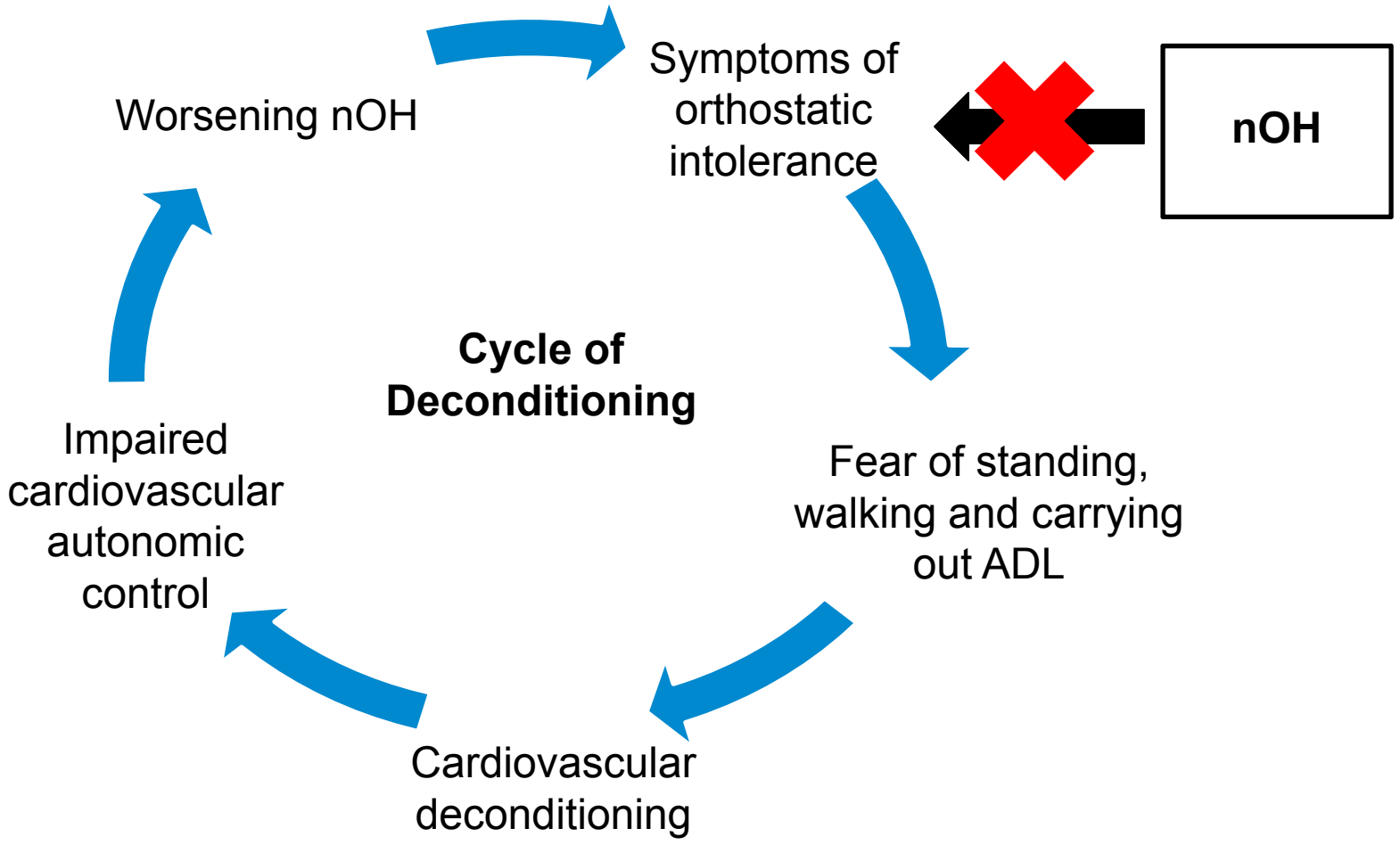


Cycle of Cardiovascular Autonomic Deconditioning



A Treatment Paradigm: Short-term Treatment Breaks the Cycle



Neurogenic Orthostatic Hypotension: Symptoms

Symptoms

- Dizziness, lightheadedness, feeling faint, or feeling like you might black out

Neurogenic Orthostatic Hypotension: Symptoms

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- Dizziness, lightheadedness, feeling faint, or feeling like you might black out
- Problems with vision
- Weakness
- Fatigue
- Trouble concentrating
- Head/neck discomfort

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- Head/neck discomfort

Symptoms Impact on Daily Activities That Require:

- Standing for a short time
- Standing for a long time
- Walking for a short time
- Walking for a long time

Kaufmann et. al, 2012, The Orthostatic Hypotension Questionnaire (OHQ): Validation of a Novel Symptom Assessment Scale

nOH is Associated with Serious Morbidity

- Increased risk of fractures and head trauma
- Fear of falling limits physical activity
  - Depression[1]
  - Social isolation[2]
  - Reduced quality of life[3]
- Decreased physical activity leads to deconditioning further worsening orthostatic tolerance[1,2]

[1]Sclater and Alagiakrishnan, *Geriatrics* 2004, August; 59(8): 22-7
[2]Vellas et al, *Age and Ageing* 1997, September, 26: 189-19
[3]Mathias, *Clin Auton Res* 2008, 18[Suppl 1]: 25–292008

nOH is Associated with Serious Morbidity

- 31 patients with neurodegenerative disease and nOH vs 26 patients without nOH
- 10 serious events over 19 days in the group with nOH
  - 7 fractures due to falls
  - 1 one severe dehydration
  - 2 cases of head trauma leading to confusion.
- No serious events in the group without nOH

Pathak et al, *Mov Disord* 2005 Sep; 20(9):1213-9

Treatment of nOH: Limited Therapeutic Options

Non-Pharmacologic:

- Increase fluid/salt
- Compression garments

Pharmacologic:

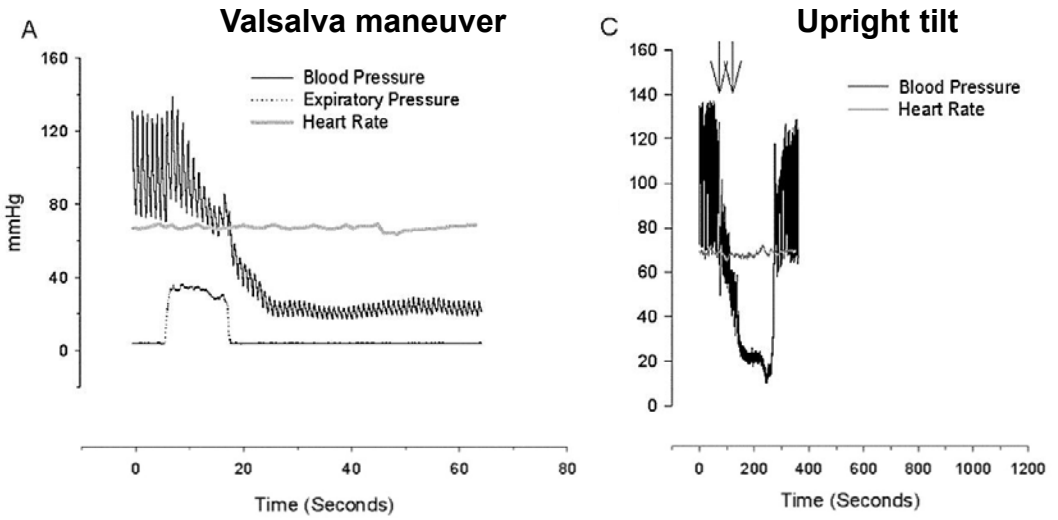
- Midodrine: direct α_1-agonist
  - Side effects: supine hypertension, paresthesias, pruritus, urinary retention, piloerection and chills
- Fludrocortisone: synthetic mineralocorticoid
  - Volume expansion; increases blood pressure
  - Side effects: supine hypertension, edema, congestive heart failure, cardiotoxicity, hypokalemia

Illustrative Case

- A 46-year-old healthy female noticed progressive, severe lightheadedness over 2 months
- She also reported dry mouth, bowel hypomotility, and urinary urgency
- Evaluation after a syncopal event revealed dilated unreactive pupils
- Supine blood pressure was 140/80 mmHg and standing blood pressure 60/40 mmHg
- Reflexes were normal and sensory examination unremarkable
- Antibodies titers to the nicotinic acetylcholine receptor of the autonomic ganglia markedly elevated at > 3000 pmol/L (ref value <50 pmol/L)

Illustrative Case

On Maximum Standard Treatment

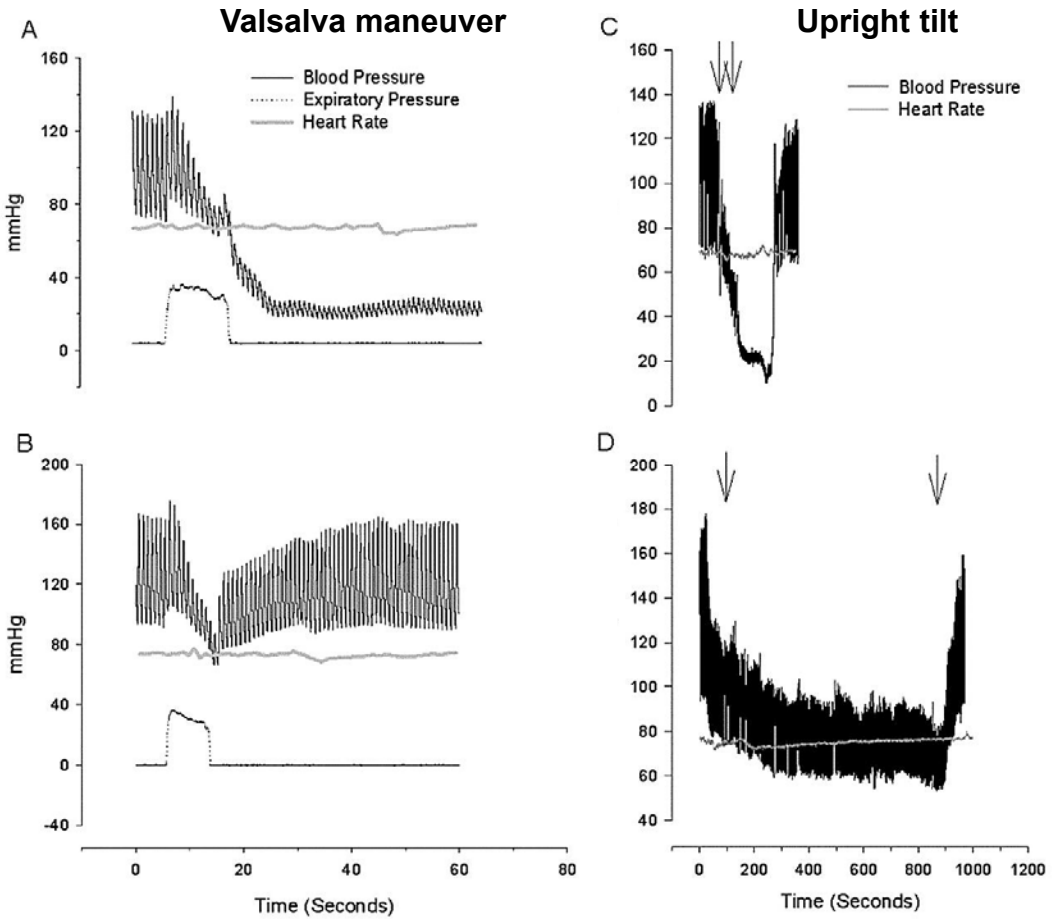


- Salt and fluid loading
- Fludrocortisone (0.3 mg qd)
- Erythropoietin (3000 units three times a week)
- Vasopressin
- Midodrine (40 mg qid)

Illustrative Case

On Maximum Standard Treatment

On Maximum Standard Treatment and Droxidopa

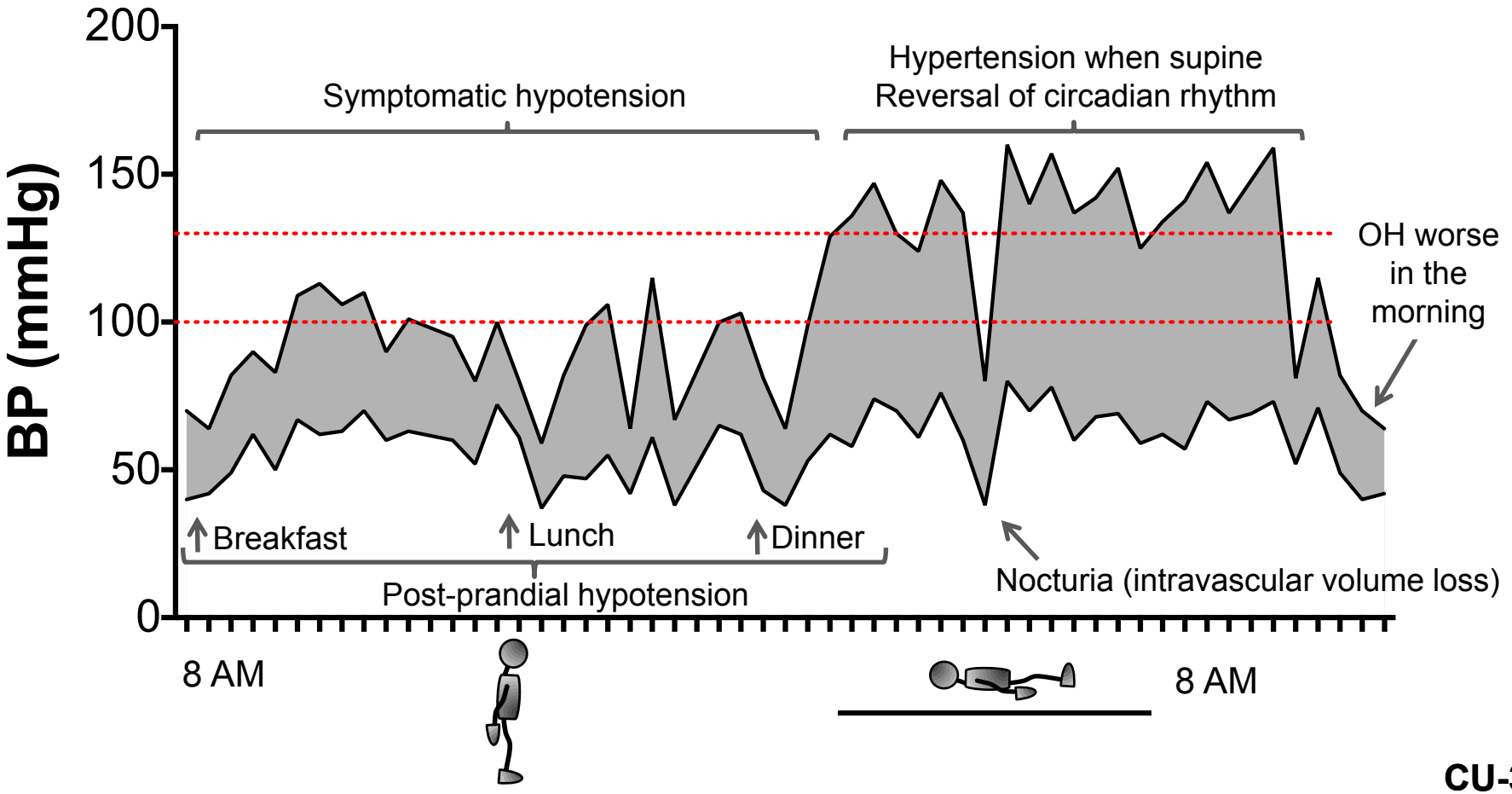


L-DOPS therapy for refractory orthostatic hypotension in autoimmune autonomic neuropathy
Gibbons, C. H. et al. Neurology 2005;65:1104-1106

Challenges in nOH Clinical Trials

Challenges in nOH Clinical Trials

- Pronounced blood pressure variability



Challenges in nOH Clinical Trials

- Efficacy signal masked by background “noise”:
  - Variable BP
  - Marked dependence of orthostatic tolerance on even small changes in intravascular volume and physical activity
  - Patient heterogeneity
  - Progression of underlying neurological disease
  - The placebo effect and cardiovascular autonomic deconditioning
- Challenges inherent to Patient Reported Outcomes (PROs)
- Orphan diseases: trials difficult to recruit

Conclusions

- nOH is a serious and disabling orphan condition
- Difficult condition to study
- Current treatment options inadequate for many patients
  - Poor efficacy
  - Intolerable side-effects
- Need for additional safe and effective therapies

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Symptomatic nOH:
Safety and Efficacy Studies

Short-Term Placebo-Controlled Studies

- Study 301: Primary endpoint - OHQ Composite at Week 1
- Study 302: Primary endpoint - Dizziness at Week 2
- Study 306B: Primary endpoint - Dizziness at Week 1

Long-Term Placebo-Controlled Studies

- Study 303: 12+ month open-label with randomized phase
- Study 306A (Interim Analysis Dataset): Primary endpoint - OHQ Composite at Week 8

Additional Studies

Supportive Studies

- Study 304: 24+ months, open-label, long-term safety study
- Study 305: 24-hour ambulatory BP monitoring study
- Study 102: Thorough, dedicated QTc study

Additional Studies

Chelsea Studies

- Study 101: Bioequivalence, PK, Fast-Fed
- Study 104: Bioequivalence, PK
- Study 201: Phase 2 study of intradialytic hypotension

Dainippon Sumitomo Studies

- S10002/ S10002a: Phase 2 EU Study in MSA and PD with follow-on
- 2034/ 2175: Phase 2 Study in FAP with follow-on
- 2034/ 2175: Phase 2 Study in FAP with follow-on

Orthostatic Hypotension Questionnaire:
Measure of Symptomatic Benefit

Symptoms

1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out
2. Problems with vision
3. Weakness
4. Fatigue
5. Trouble concentrating
6. Head/neck discomfort

OHSA Composite

Symptom Impact on Daily Activities That Require:

1. Standing for a short time
2. Standing for a long time
3. Walking for a short time
4. Walking for a long time

OHDAS Composite

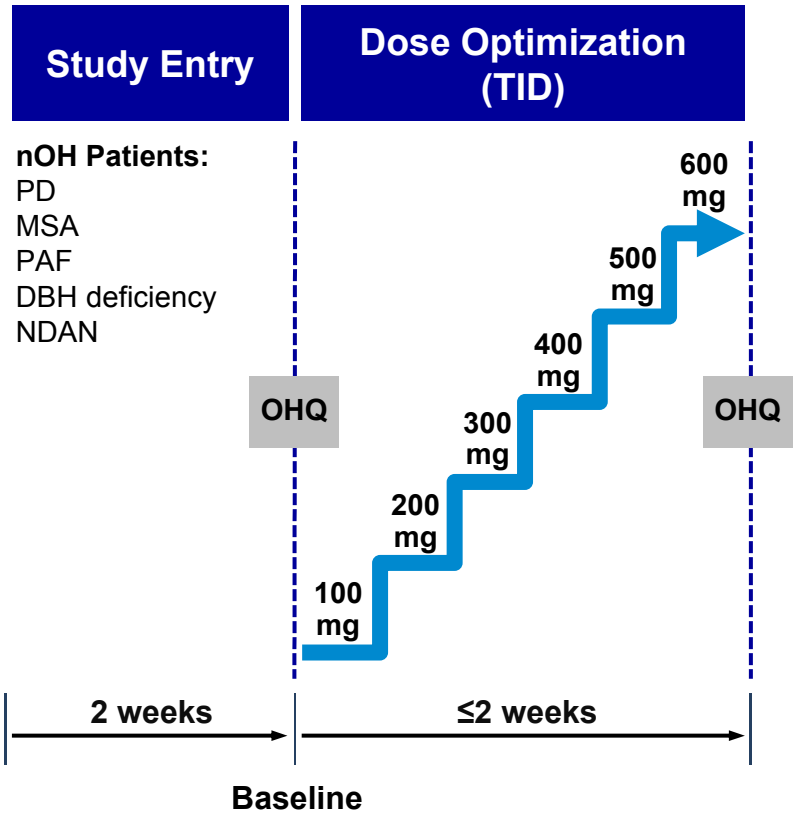
OHQ Composite

Agenda:
Efficacy Results

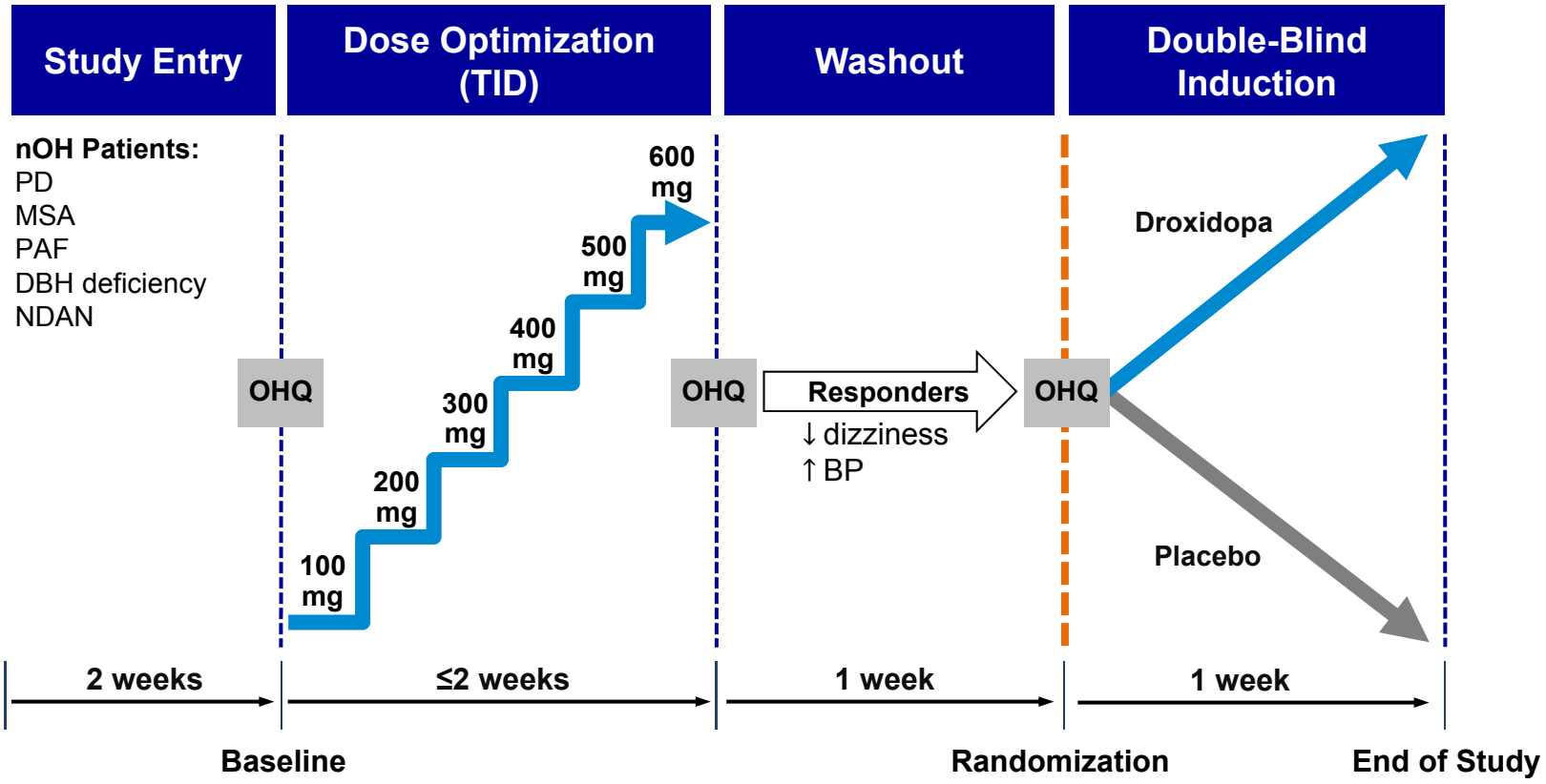
- Study 301
- Study 302
- Study 306B
- Data Durability
- Other Blood Pressure Studies
- Integrated Summary of Efficacy

Study 301

Study 301:
Study Design



Study 301:
Study Design



Study 301:
Study Design

- Phase 3, multi-center, multi-national, double-blind, randomized, placebo-controlled, parallel-group induction-design study
- Primary endpoint: mean change in OHQ composite score (Randomization to End of Study)
- Full Analysis Set: 80 placebo, 82 droxidopa
- Safety Set: 81 placebo, 81 droxidopa
- Total of 94 sites across 9 countries

Study 301:
Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Clinical diagnosis of OH associated with primary autonomic failure (PD, MSA, and PAF), DBH Deficiency, or NDAN
- Documented fall in standing SBP ≥20 mmHg or DBP ≥10 mmHg

Key Exclusion Criteria

- Taking vasoconstricting agents such as ephedrine, dihydroergotamine, or midodrine within 2 days of study entry
- Taking anti-hypertensive medication (use of short-acting, anti-hypertensive medications at bedtime were permitted)
- Pre-existing severe supine hypertension: BP ≥180/110 mmHg
- Significant systemic, hepatic, cardiac, or renal illness
- Diabetes mellitus or insipidus
- Mental disorder that interfered with the diagnosis and/or conduct of study

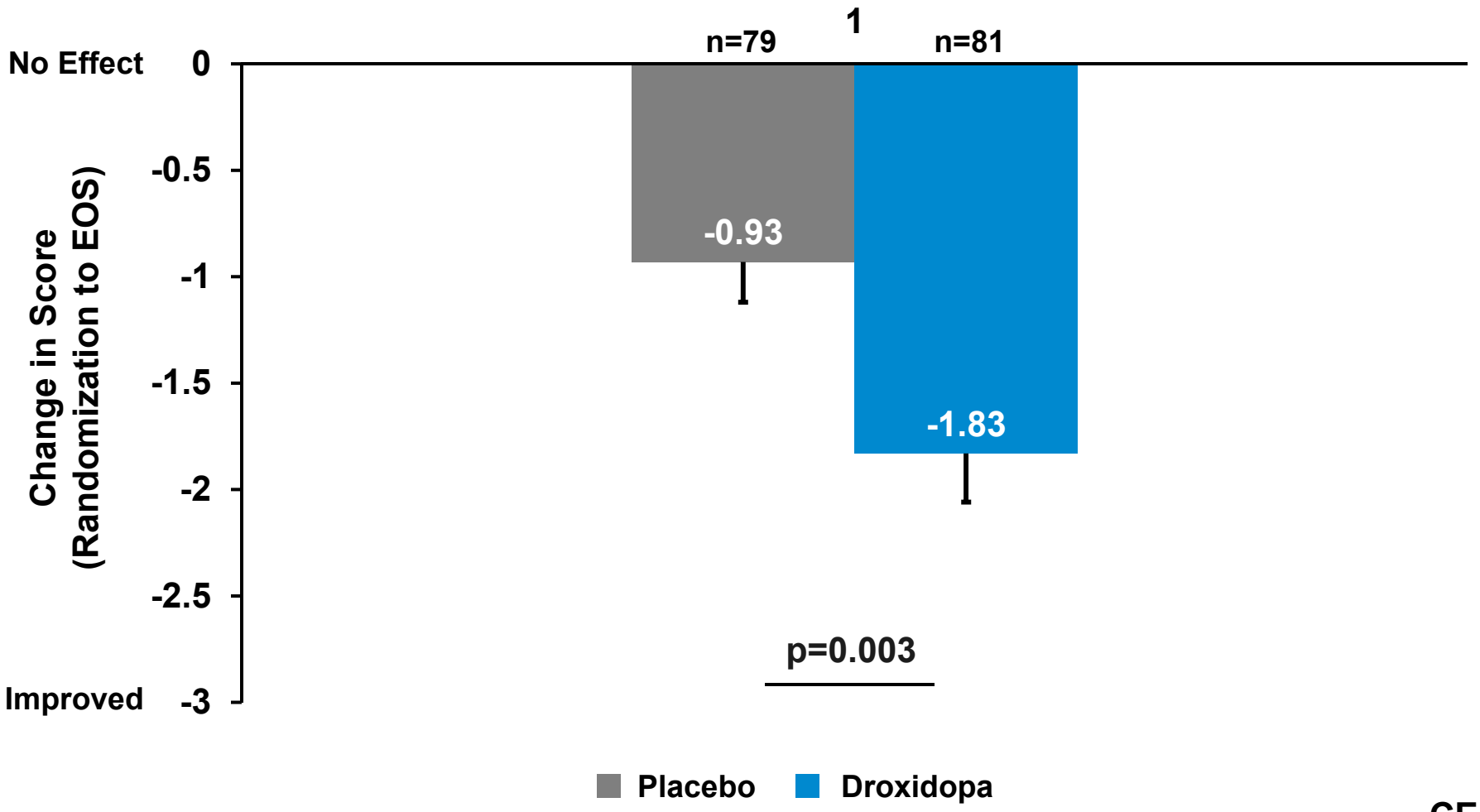
Study 301:
Patient Demographics

		Randomized-Controlled Phase	
		Placebo N=81	**Droxidopa N=81**
Primary Diagnosis: n (%)	PD	31 (38.3)	35 (43.2)
	PAF	28 (34.6)	26 (32.1)
	MSA	12 (14.8)	14 (17.3)
	Non-Diabetic Autonomic Neuropathy	6 (7.4)	2 (2.5)
	Other Diagnosis	4 (4.9)	4 (4.9)
Sex: n (%)	Male	43 (53.1)	41 (50.6)
	Female	38 (46.9)	40 (49.4)
Race: n (%)	White	76 (93.8)	81 (100.0)
	Other	5 (6.2)	0
Age at Screening	Mean [range]	55.8 [18,87]	57.3 [20,84]
Geographic Region: n (%)	US	33 (40.7)	32 (39.5)
	Non-US	48 (59.3)	49 (60.5)
Baseline Disease Severity	Mean OHQ Composite Score, units [range]	5.6 [1.2, 9.8]	6.0 [2.0, 9.6]
	Mean Dizziness Score, units [range]	6.2 [1,10]	6.5 [3,10]
	Mean Standing SBP, mmHg (SD)	90.7 (16.83)	90.8 (15.63)

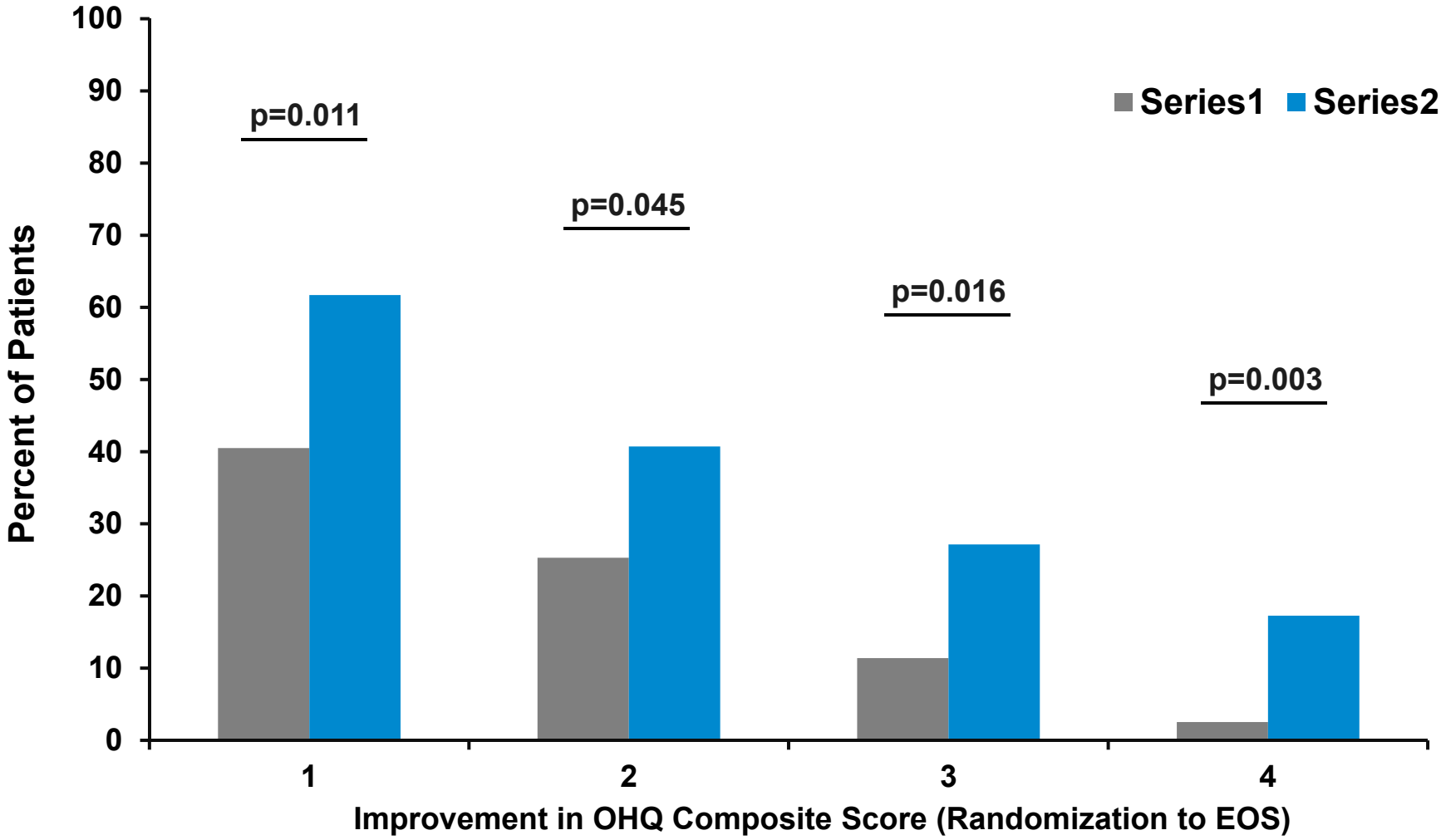
Study 301:
Concomitant Medications

ATC Class	Randomized-Controlled Phase	
	Placebo (N=81) n (%)	Droxidopa (N=81) n (%)
Any Concomitant Medication	**61 (75.3)**	**63 (77.8)**
DOPA and DOPA Derivatives	32 (39.5)	32 (39.5)
Mineralocorticoids	18 (22.2)	21 (25.9)
Platelet Aggregation Inhibitors Excl. Heparin	21 (25.9)	17 (21.0)
Selective Serotonin Reuptake Inhibitors	17 (21.0)	16 (19.8)
Dopamine Agonists	11 (13.6)	13 (16.0)
Monoamine Oxidase B Inhibitors	8 (9.9)	12 (14.8)
HMG CoA Reductase Inhibitors	14 (17.3)	11 (13.6)
Proton Pump Inhibitors	13 (16.0)	11 (13.6)
Anticholinesterases	9 (11.1)	10 (12.3)
Thyroid Hormones	12 (14.8)	9 (11.1)

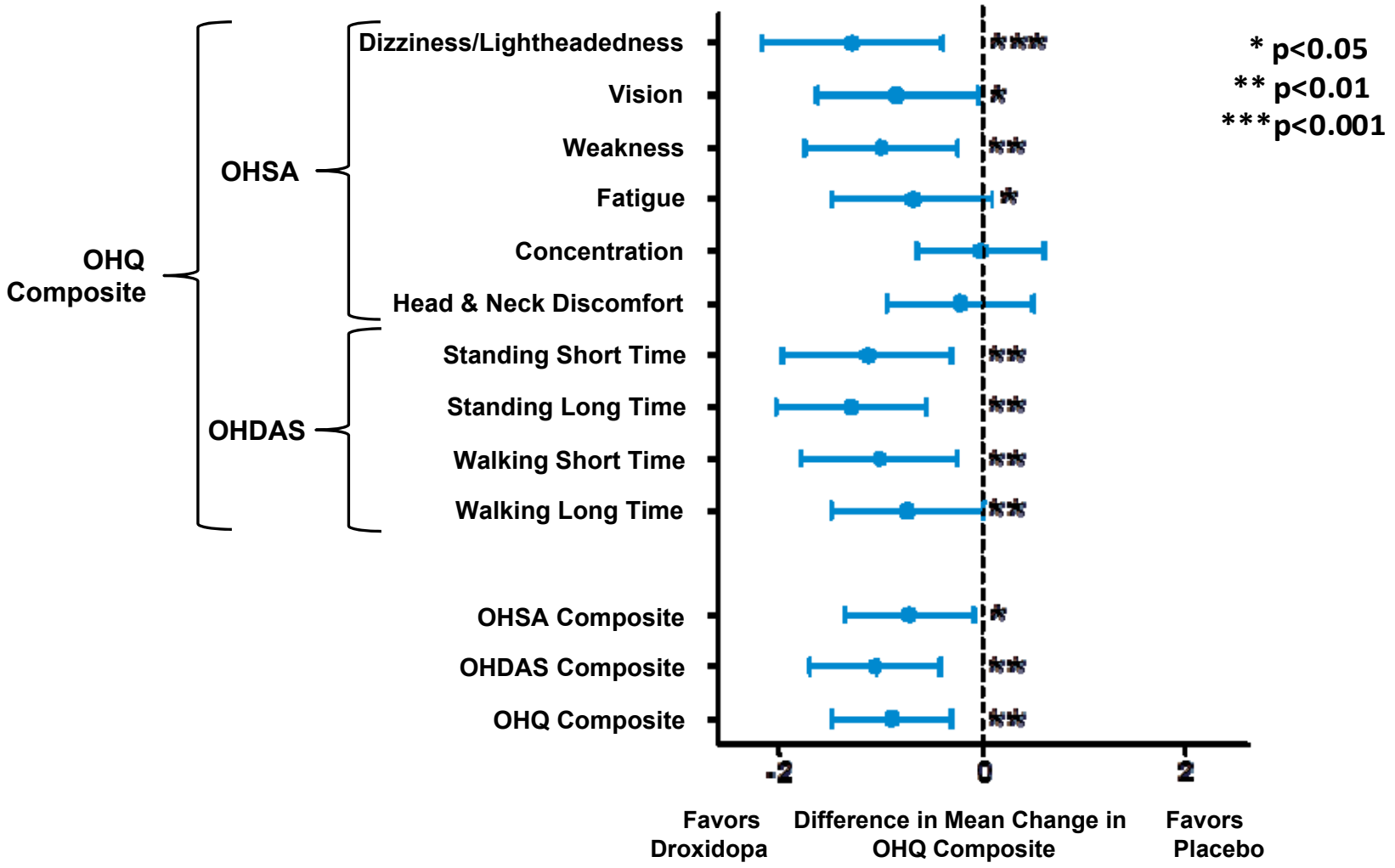
Study 301:
OHQ Composite



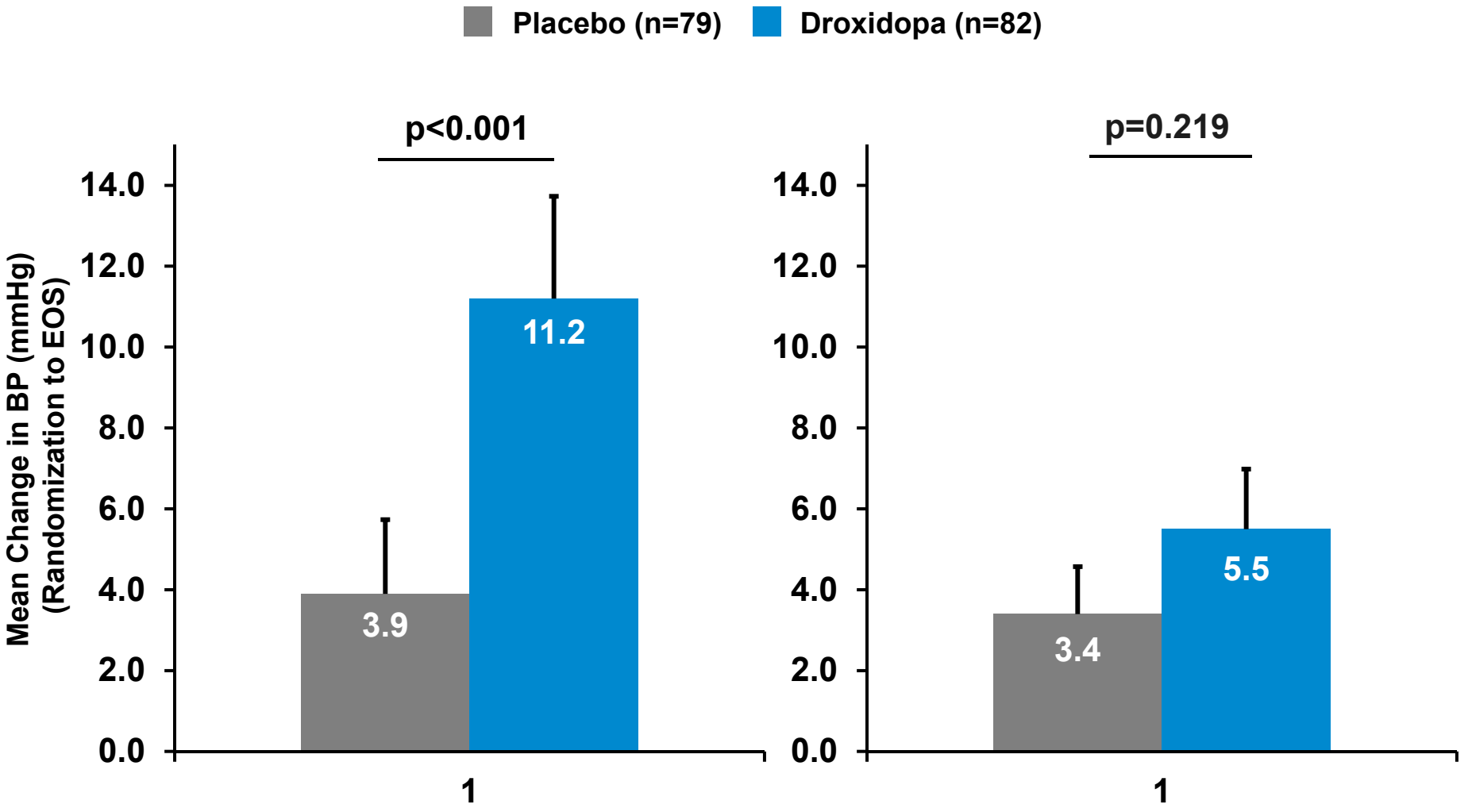
Study 301: Magnitude of Effect
OHQ Composite Score



Study 301:
OHQ Components



Study 301:
Increase in Standing Blood Pressure



Study 301:
Hierarchy of Efficacy Endpoints

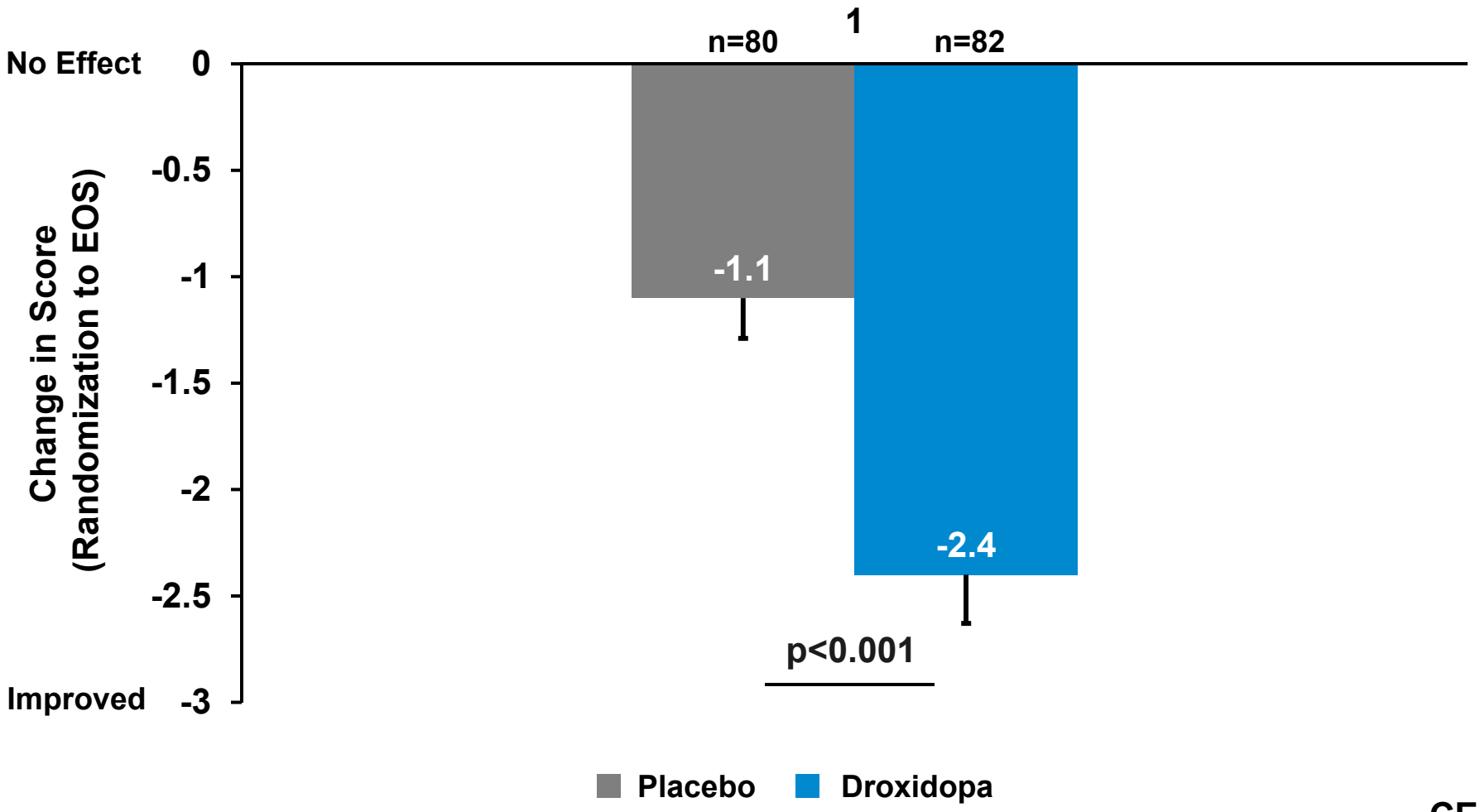
Study 301 Efficacy Endpoints	Treatment Difference Favoring Droxidopa	p-value
Primary Efficacy Endpoint		
OHQ Composite Score	-0.9	0.003
Secondary Efficacy Endpoints		
OHDAS Composite Score	-1.1	0.003
OHSA Composite Score	-0.7	0.010
OHDAS Item 1 (standing short time)	-1.1	0.003
OHDAS Item 3 (walking short time)	-1.1	0.009
OHSA Item 1 (dizziness/lightheadedness)	-1.3	<0.001

Regulatory Guidance:
Primary Endpoints

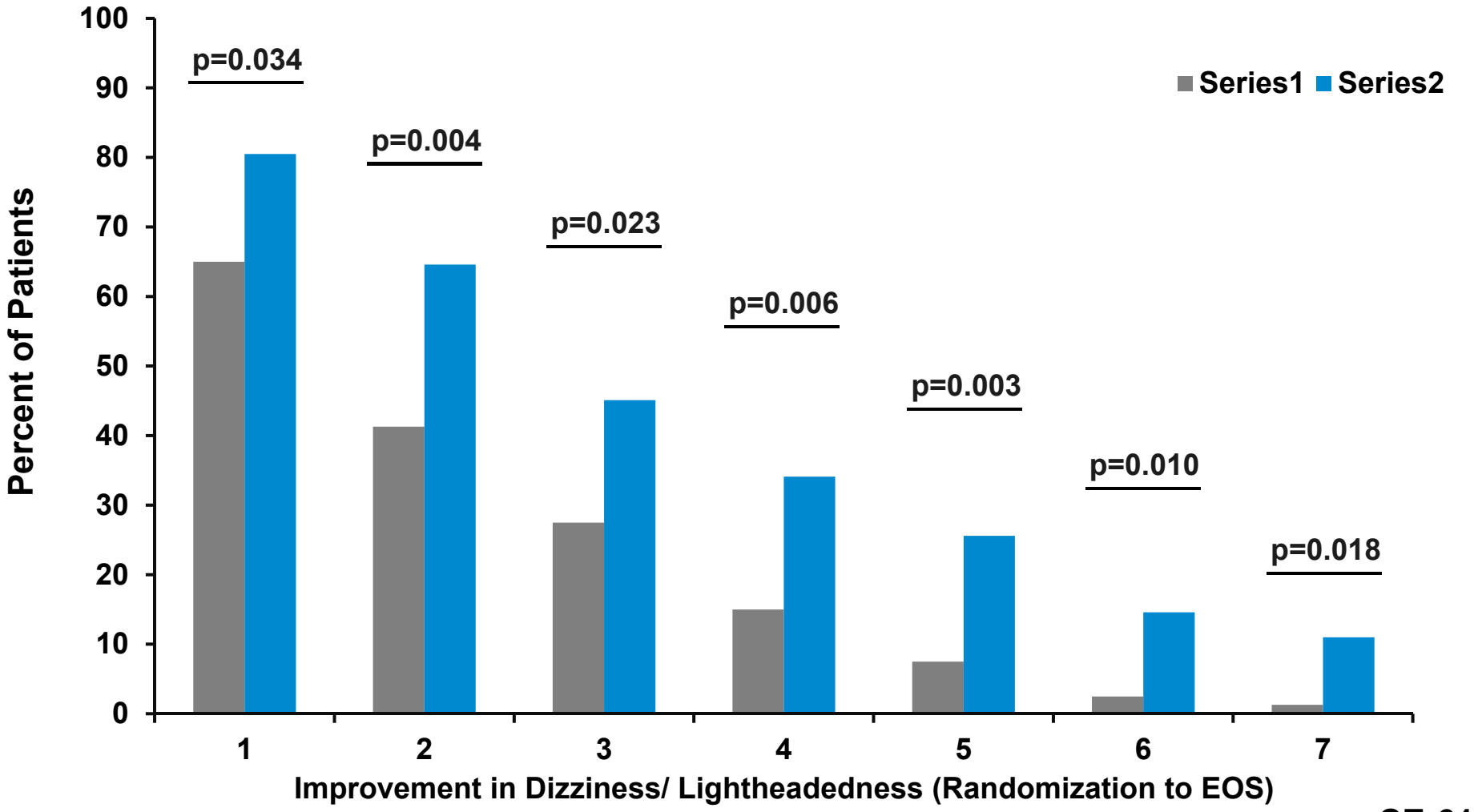
"*The OHSA Item 1, however, captures the most important symptoms of the patients who suffer from symptomatic orthostatic hypotension: dizziness, lightheadedness, feeling faint, or feeling like you might black out*."

"*The concept of OHSA Item 1 is comprehensive and unambiguous…. and therefore has content validity.*"

Study 301:
Dizziness/Lightheadedness

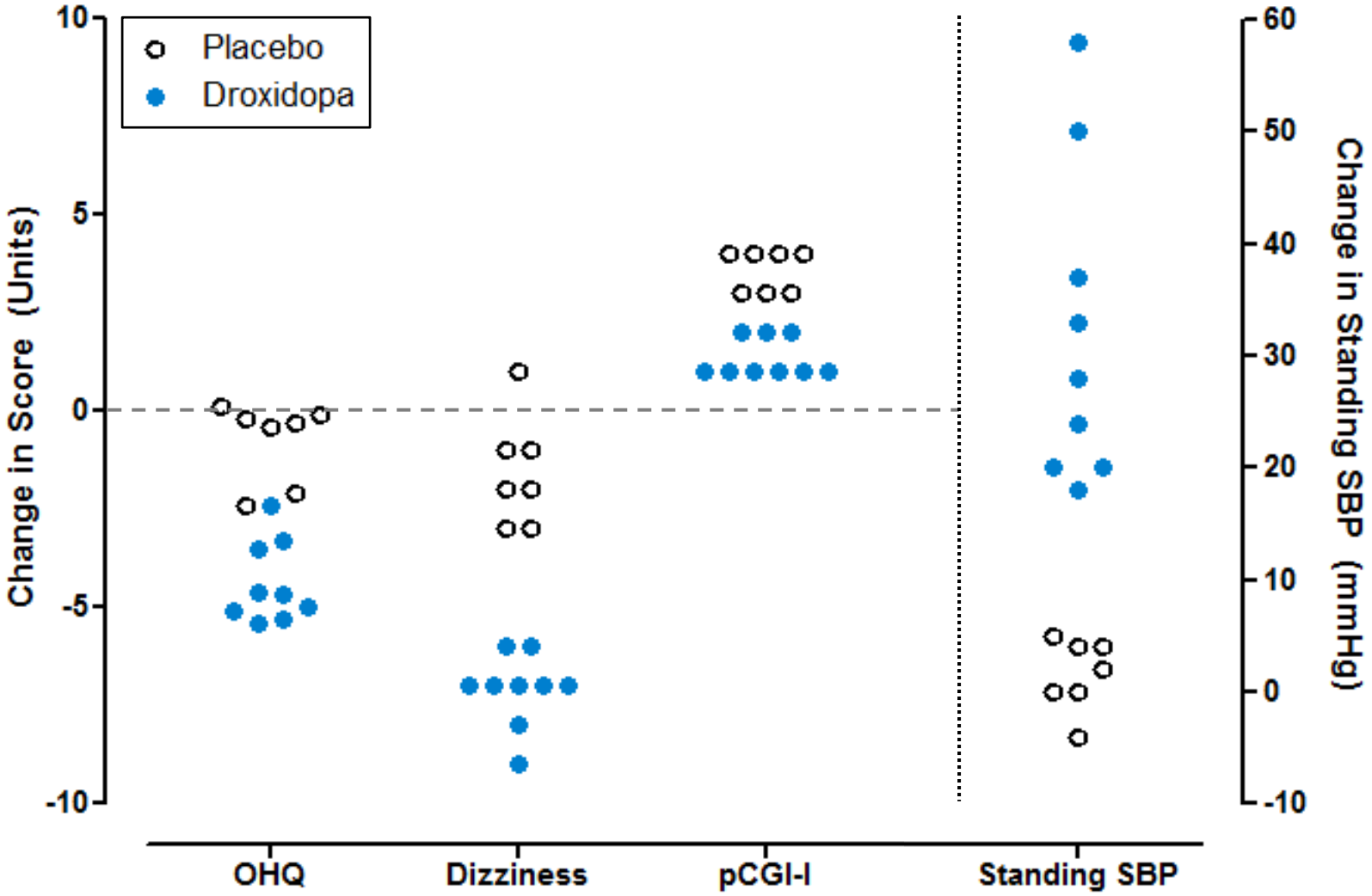


Study 301:
Dizziness/Lightheadedness Response

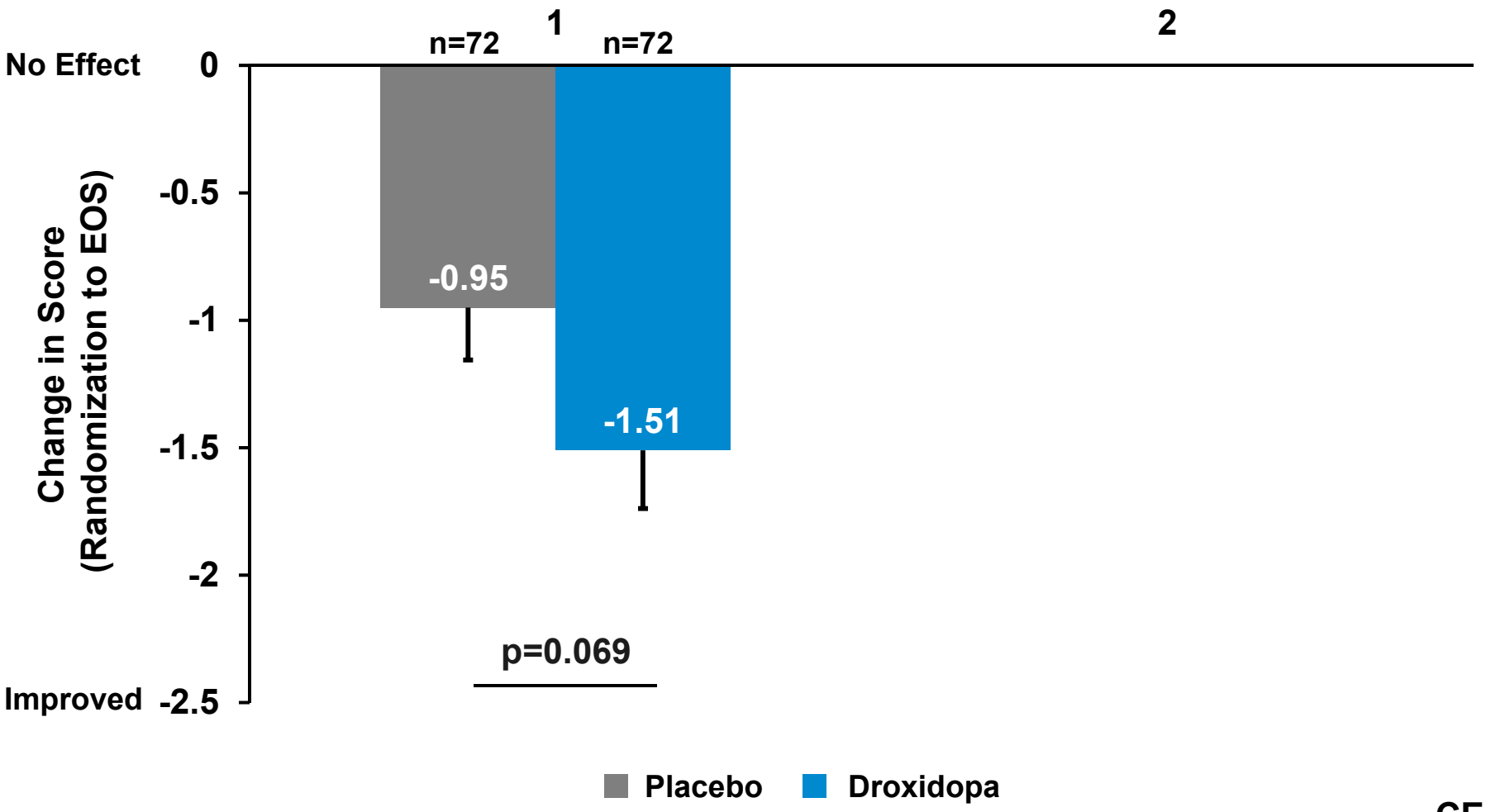


Study 301: Sensitivity Analyses
Site 507

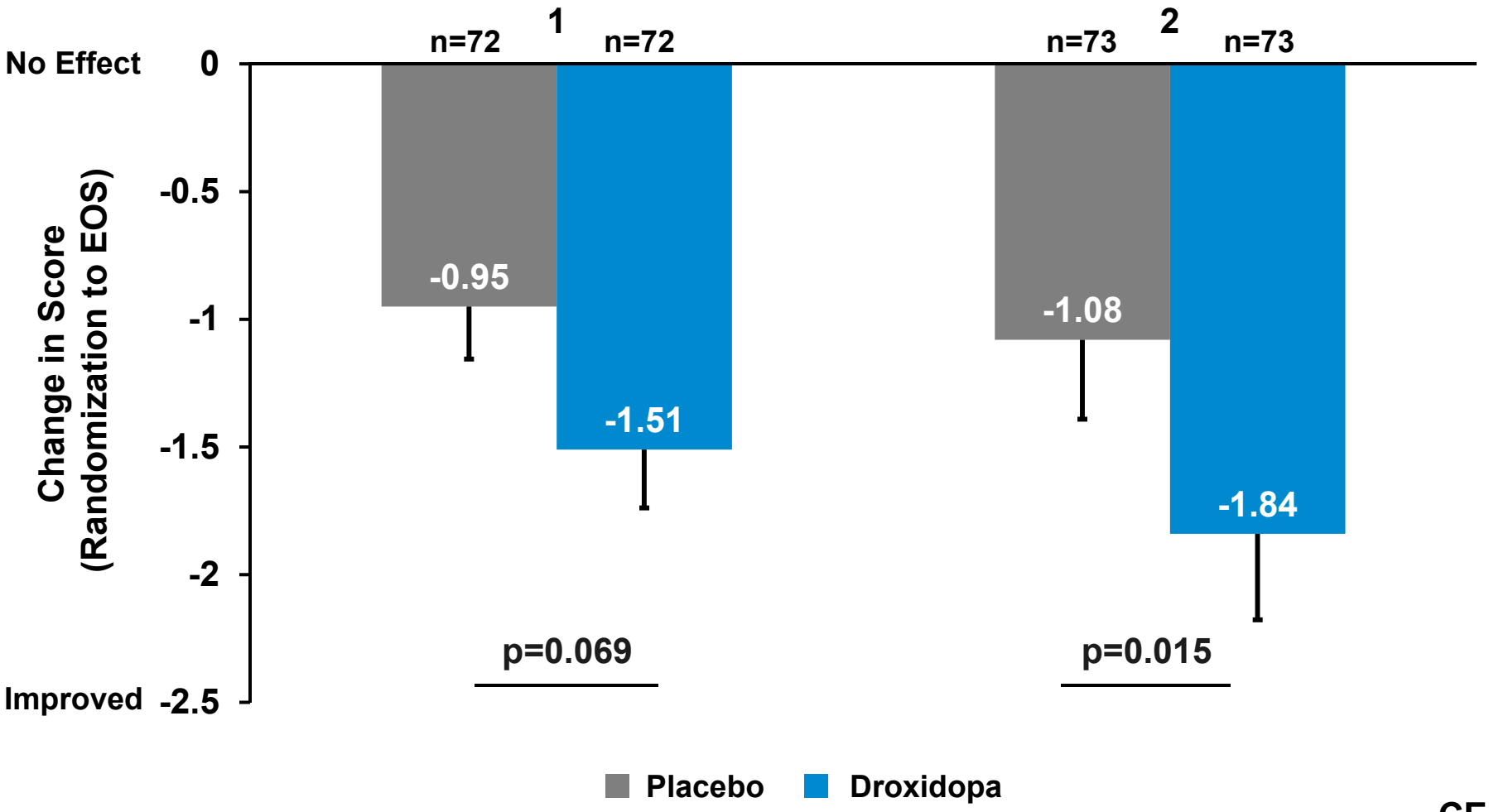
Study 301, Site 507:
Individual Patient Data



Study 301 Excluding Site 507:
OHQ Composite and Dizziness/Lightheadedness



Study 301 Excluding Site 507:
OHQ Composite and Dizziness/Lightheadedness



Study 301 Site 507:
Efforts to Ensure Data Validity

Auditor/Activity	Date	Major Findings
Routine Monitoring During Study		
Contract Research Organization	28 Apr 2009	none
Contract Research Organization	18-19 May 2009	none
Contract Research Organization	12 Jun 2009	none
Contract Research Organization	23-24 Jun 2009	none
Contract Research Organization	8-9 Jul 2009	none
Contract Research Organization	17 Jul 2009	none
Contract Research Organization	25-26 Aug 2009	none
Contract Research Organization	30 Sep 2009	none
Independent Data Verification		
Second Contract Research Organization	1-3 Feb 2011	none
Second Contract Research Organization	11-13 Oct 2011	none
Second Contract Research Organization	26 Dec 2011	none

Study 301 Site 507:
Efforts to Ensure Data Validity

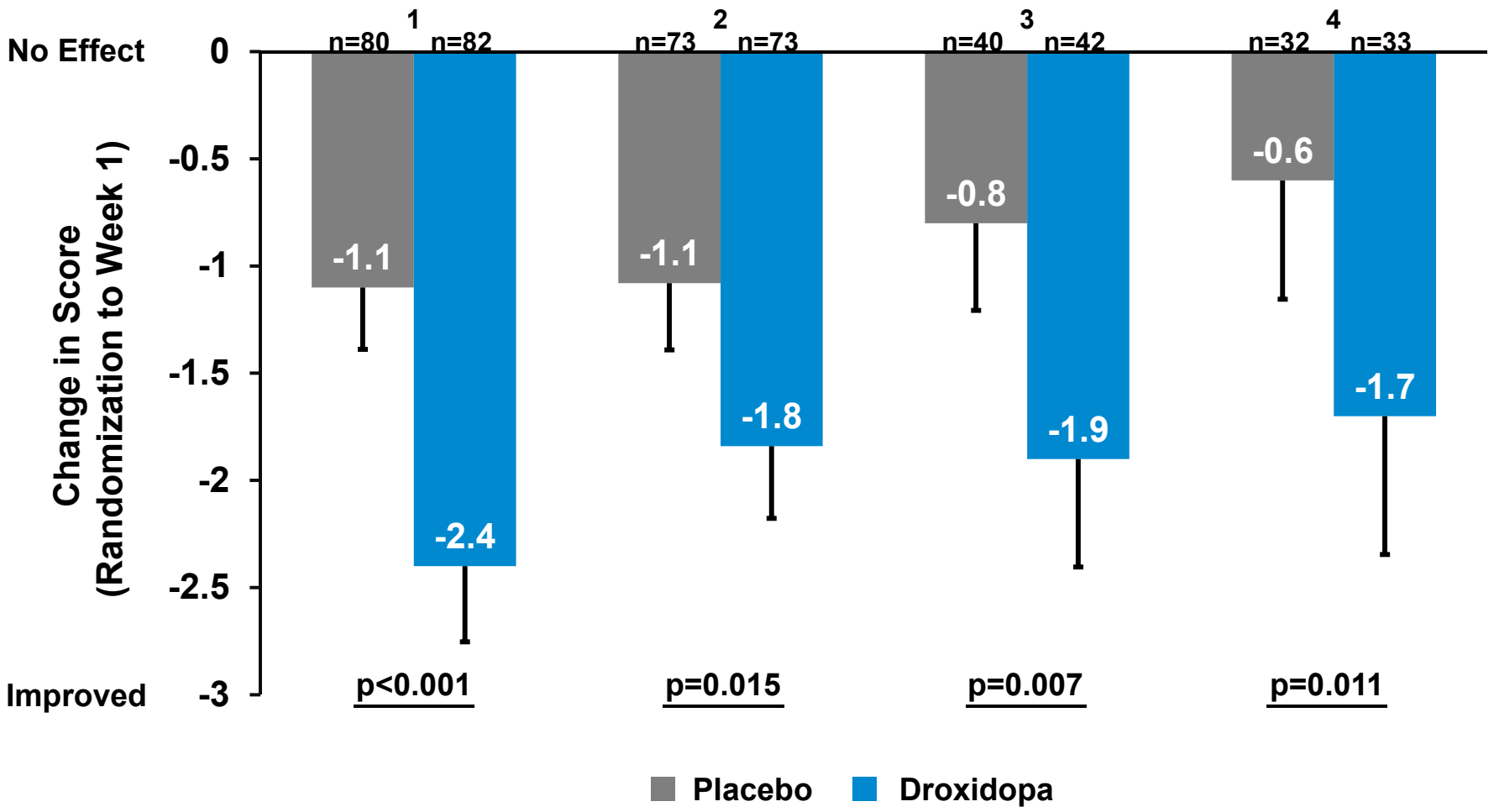
Auditor/Activity	Date	Major Findings
Routine Monitoring During Study		
Contract Research Organization	28 Apr 2009	none
Contract Research Organization	18-19 May 2009	none
Contract Research Organization	12 Jun 2009	none
Contract Research Organization	23-24 Jun 2009	none
Contract Research Organization	8-9 Jul 2009	none
Contract Research Organization	17 Jul 2009	none
Contract Research Organization	25-26 Aug 2009	none
Contract Research Organization	30 Sep 2009	none
Independent Data Verification		
Second Contract Research Organization	1-3 Feb 2011	none
Second Contract Research Organization	11-13 Oct 2011	none
Second Contract Research Organization	26 Dec 2011	none
Sponsor Visits and Audits		
Sponsor Site Visit	16 Jul 2009	none
CRO Quality Assurance Audit	25-26 Aug 2009	none
Directed Audit	5-8 Nov 2012	none
Provide Source Documents to FDA	8 Nov 2012	none
FDA Inspection Following Completion of Study 301		
FDA pre-approval inspection	20-25 Jan 2012	none

Study 301:
Site 507 Characteristics

- Lead hospital for region in Ukraine; ~3.5 million patient catchment area
- All patients naïve to pharmacologic treatment
- Majority had nOH secondary to NDAN causes (10/16, 62.5%)

Baseline Demographics	Site 507 (N=16)	Study 301 Ex-507 (N=146)
Dizziness/Lightheadedness Score	8.3	5.1
OHQ Composite Score	6.15	5.75
Standing SBP	93.3 mmHg	97.5 mmHg
Age at Screening	42.7	56.5

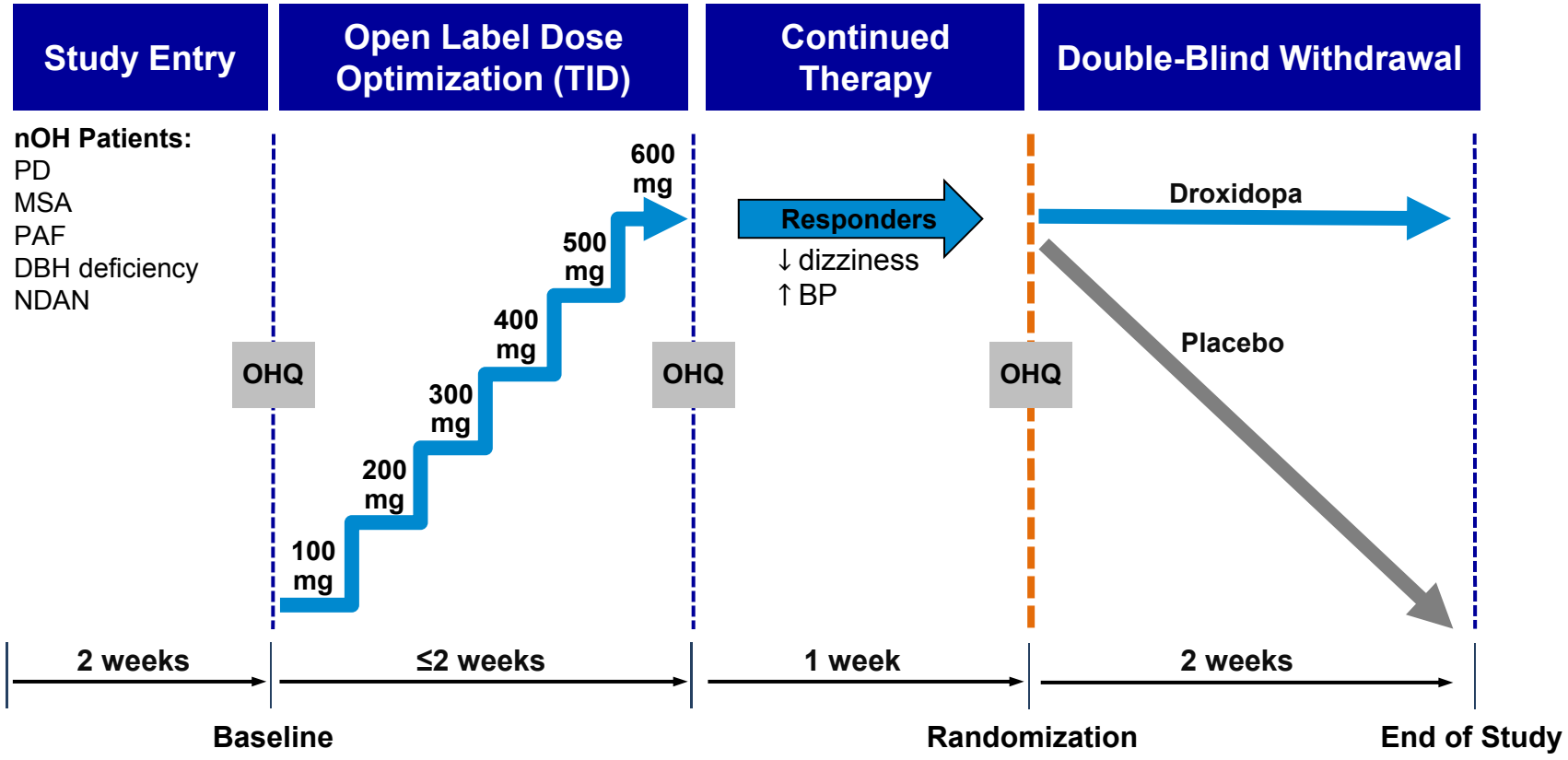
Study 301, Regional Assessment:
Dizziness/Lightheadedness at Week 1



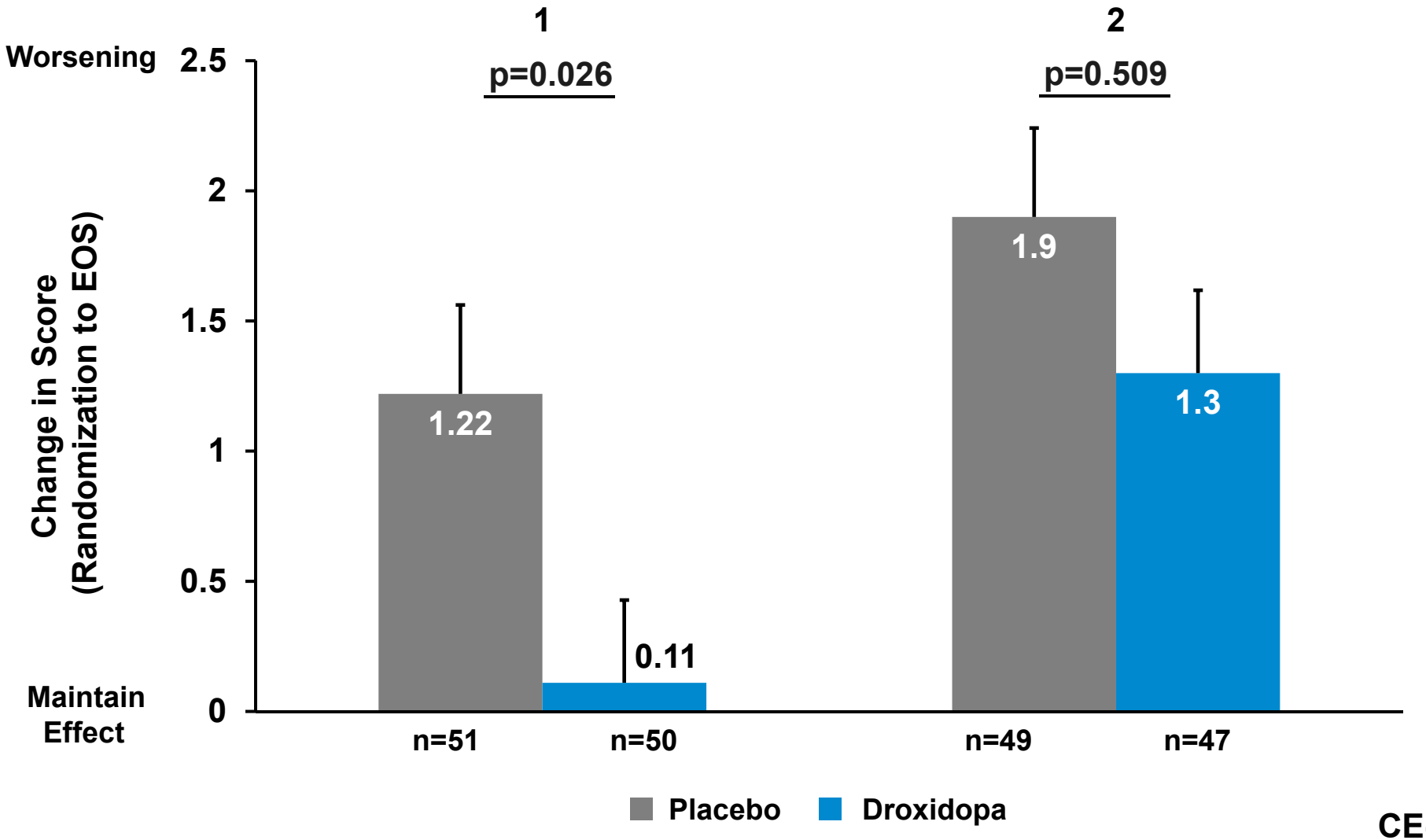
*Use of non-parametric CMH Rank ANCOVA was pre-specified

Study 302

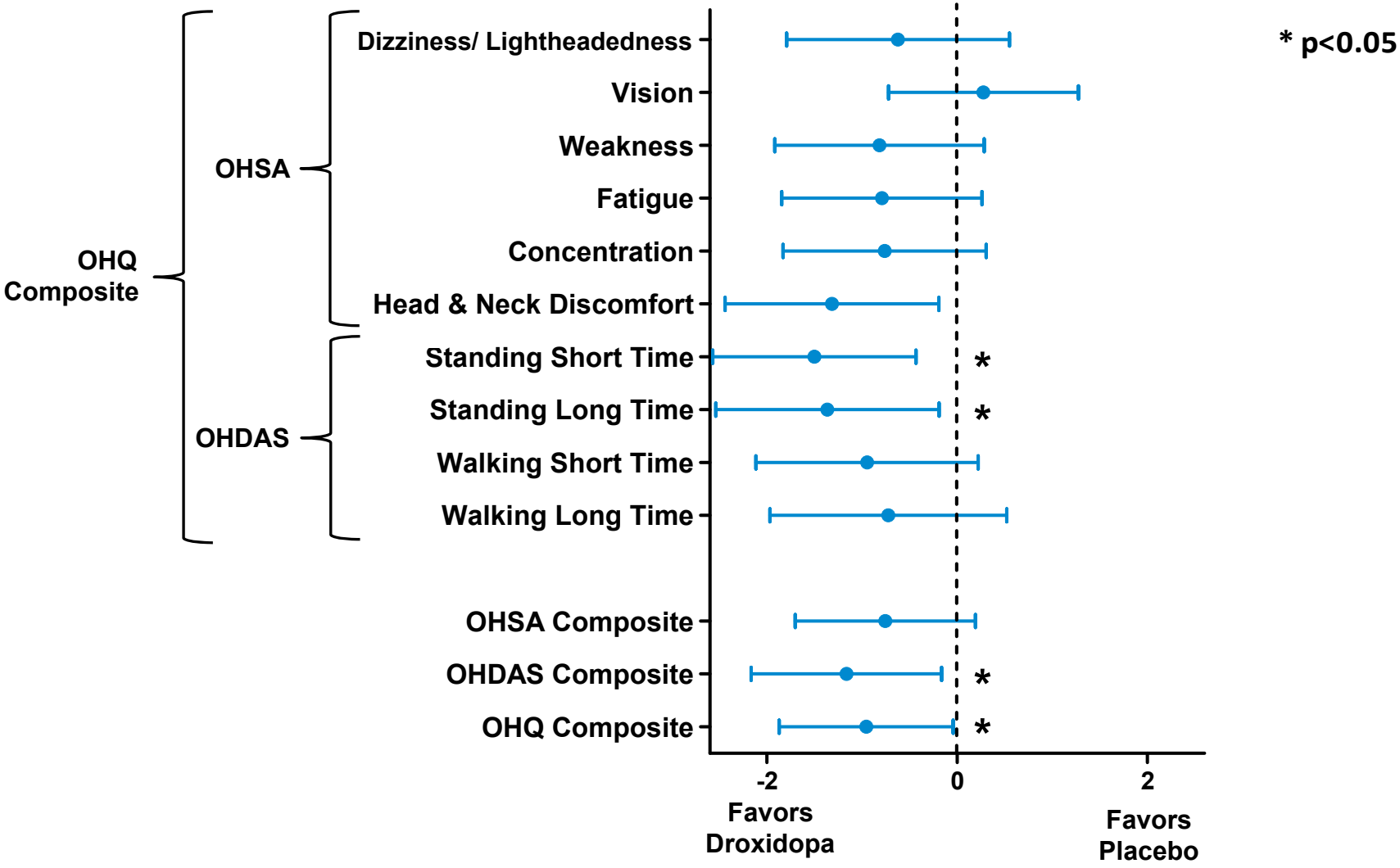
Study 302:
Study Design



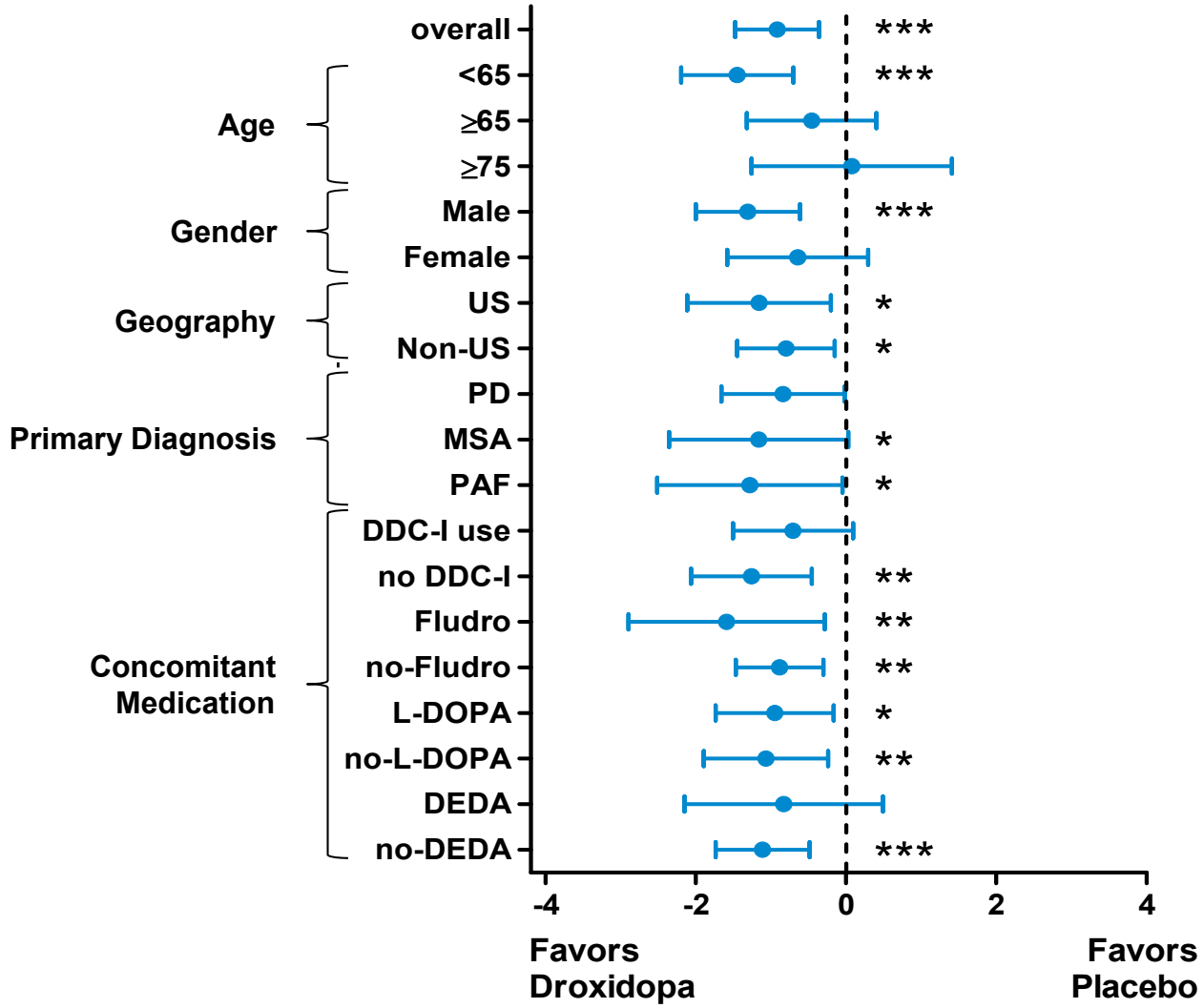
Study 302:
OHQ Composite and Dizziness/Lightheadedness



Study 302:
OHQ Components



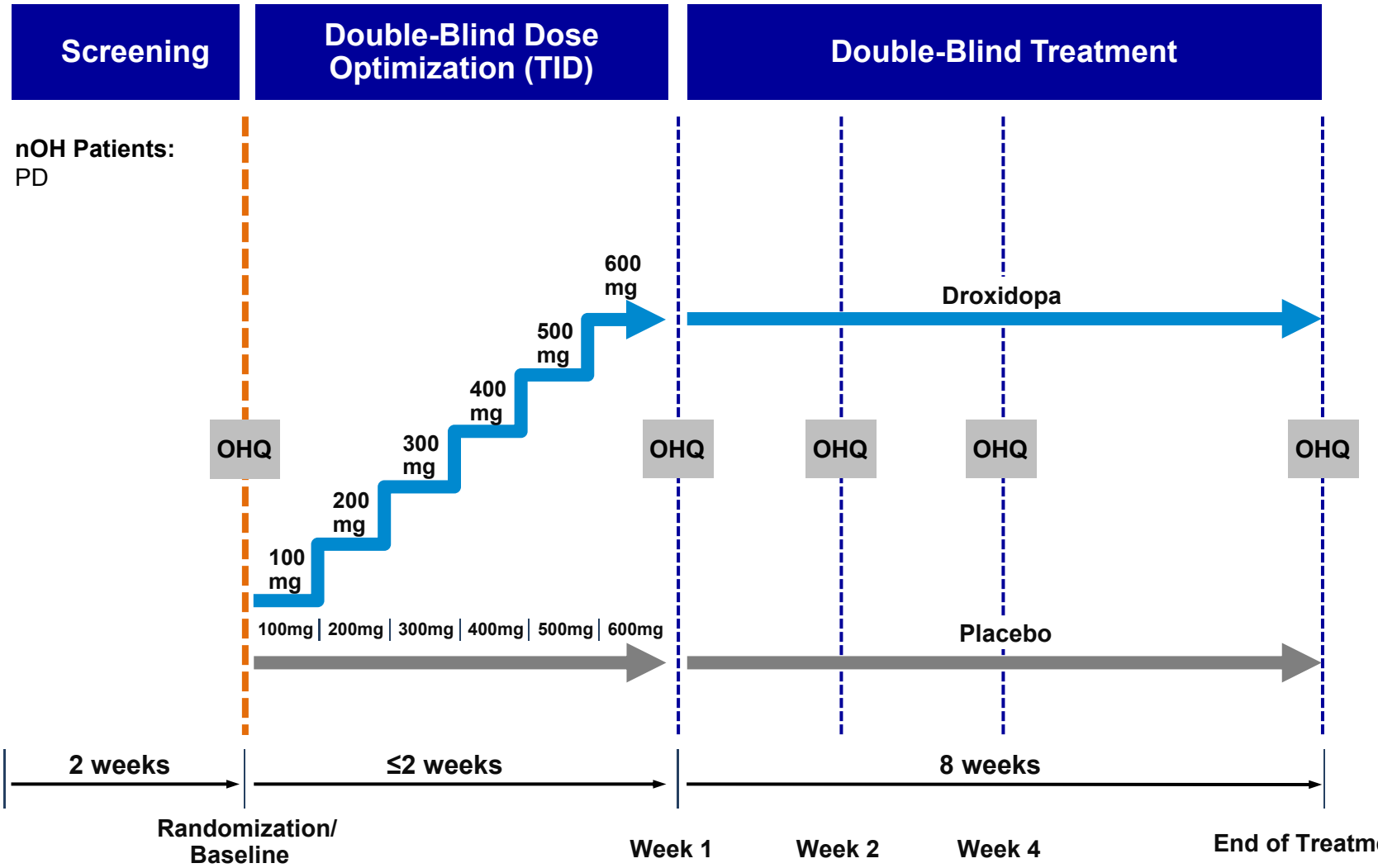
Studies 301 and 302:
Subgroup Analysis of OHQ Composite



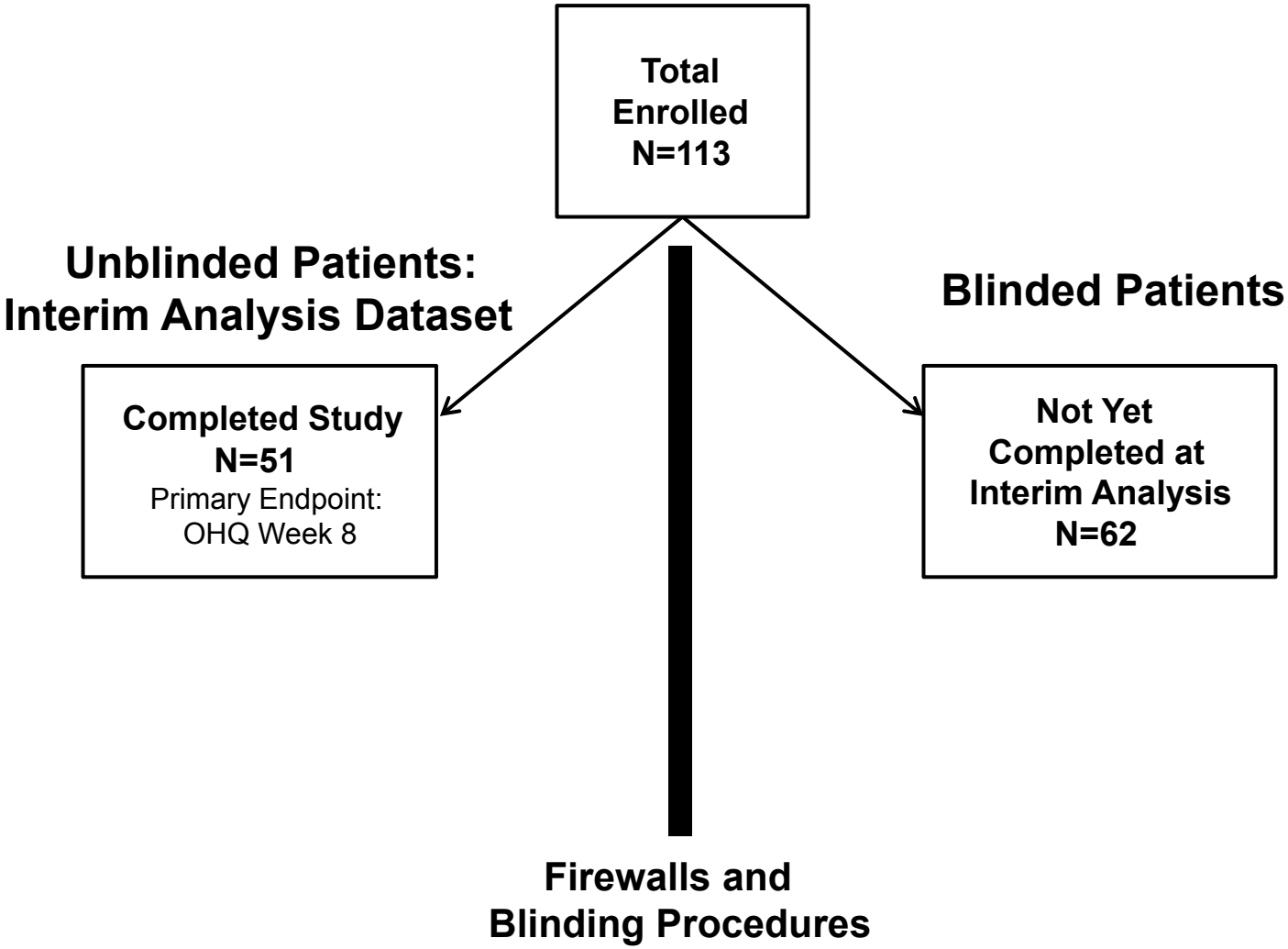
*p<0.05
** p<0.01
***p<0.001

Study 306B

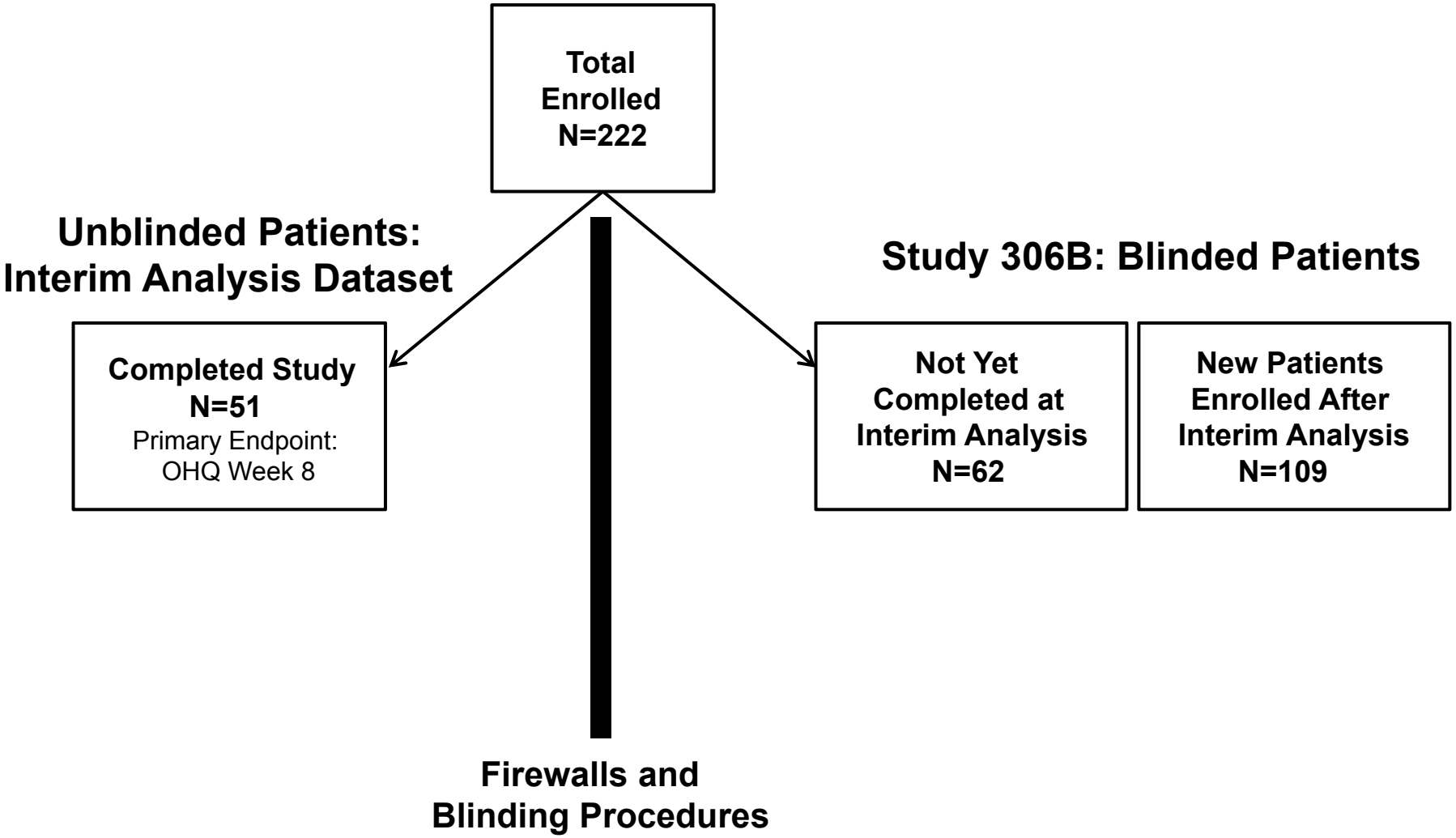
Study 306:
Study Design



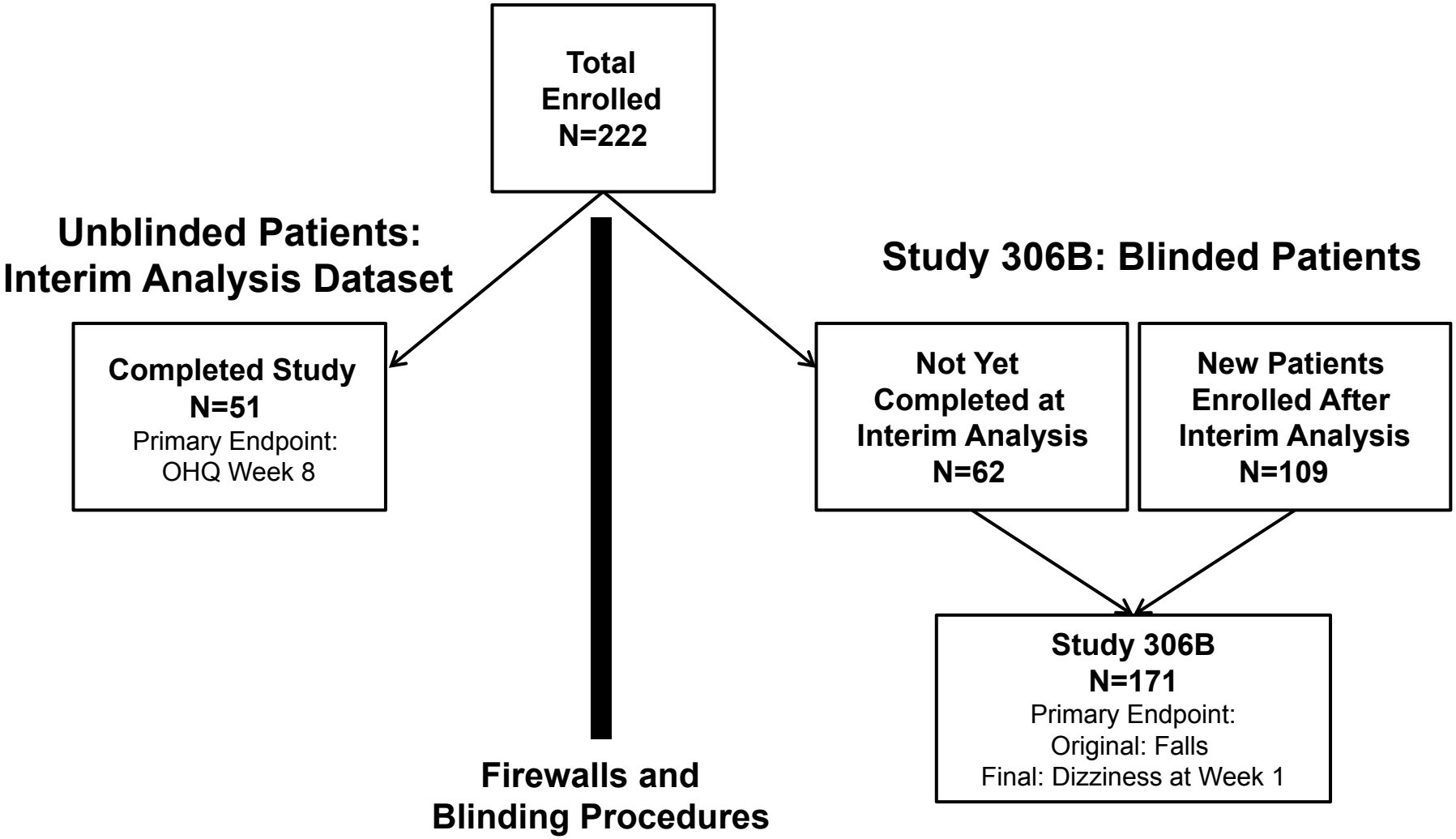
Study 306:
Interim Analysis



Study 306:
Evolution of Study 306B



Study 306:
Evolution of Study 306B



Study 306B:
Review of Blinding Documentation

Chelsea Remained Blinded to Study 306B Data

- Extensive documentation submitted to Agency
  - Timelines
  - Standard Operating Procedures
  - Processes
  - Audit Reports
  - Sworn statements from study personnel
- Reviewed by Office of Scientific Investigations, FDA
- Reviewed by Director, Office of Biostatistics, FDA
- Agency concluded Study 306B may be acceptable as a 2nd positive study

Study 306B:
Trial Design and Statistical Considerations

- Phase 3, multi-center, double-blind, randomized, placebo-controlled, parallel-group, induction design study (total of 10 weeks)
- Primary endpoint: mean change in dizziness/ lightheadedness at Week 1
- Statistical considerations
  - Target: >100 evaluable patients in each treatment group
  - Full Analysis Set: 79 placebo, 68 droxidopa
  - Safety Set: 82 placebo, 89 droxidopa

Study 306B:
Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Clinical diagnosis of PD
- Clinical diagnosis of symptomatic NOH
  - A score of at least 3 on the OHQ composite
  - A score of at least 3 on the clinician CGI-S
  - Documented fall in standing SBP ≥ 20 mmHg or DBP ≥ 10 mmHg

Key Exclusion Criteria

- Taking vasoconstricting agents such as ephedrine, dihydroergotamine, or midodrine (within 2 days of study entry)
- Taking anti-hypertensive medication (use of short-acting, anti-hypertensive medications at bedtime were permitted)
- Pre-existing severe supine hypertension: (BP ≥ 180/110 mmHg)
- Significant systemic or cardiac illness

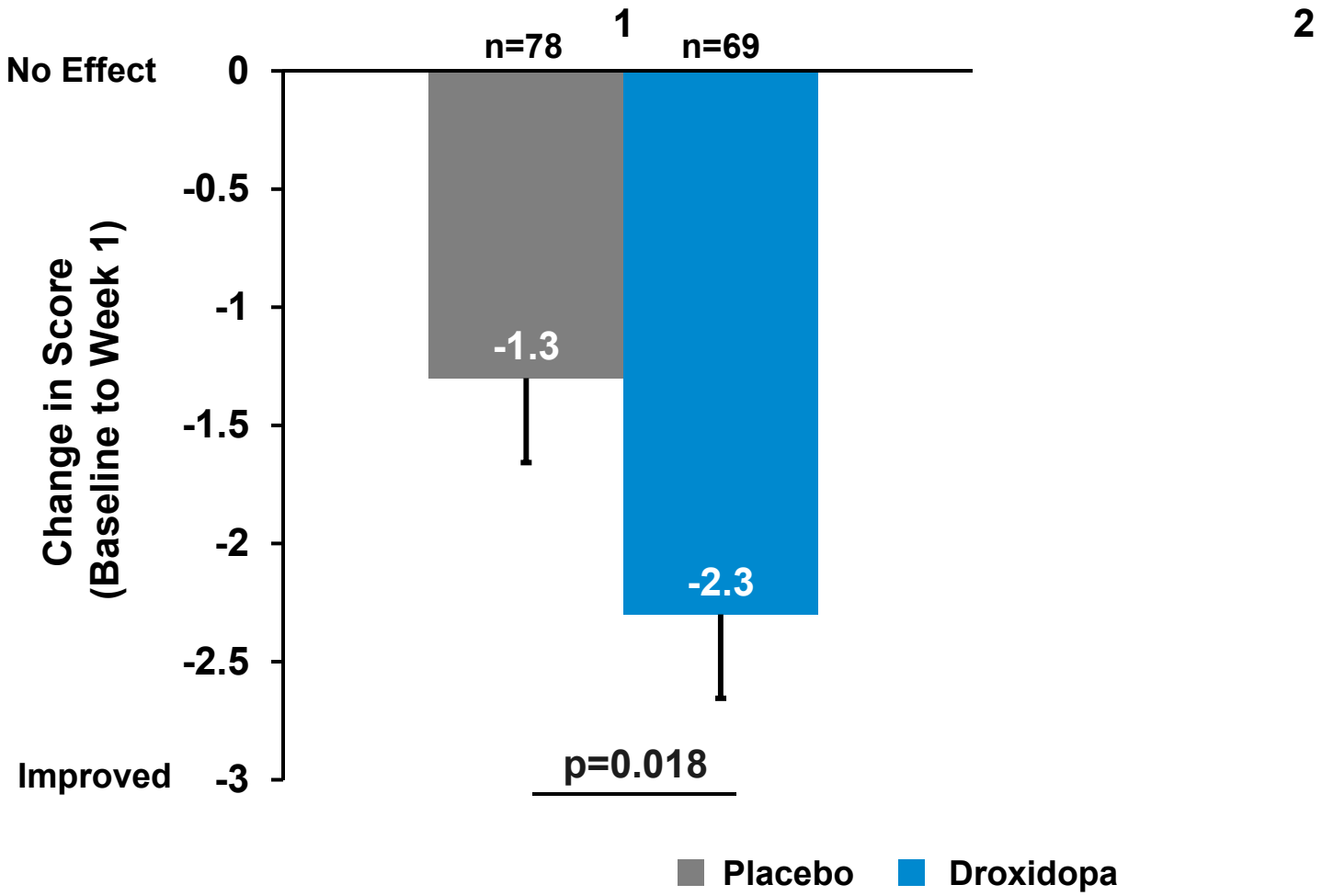
Study 306B:
Patient Demographics

		Randomized-Controlled Phase	
		Placebo (N=82)	**Droxidopa (N=89)**
Primary Diagnosis: n (%)	PD	82 (100.0)	89 (100.0)
Sex: n (%)	Male	52 (63.4)	62 (69.7)
	Female	30 (36.6)	27 (30.3)
Race: n (%)	White	79 (96.3)	85 (95.5)
	Other	3 (3.7)	4 (4.5)
Age at Screening:	Mean [range]	72.0 [53,86]	72.5 [41,92]
Geographic Region: n (%)	US	82 (100.0)	89 (100.0)
Baseline Disease Severity		**N=78**	**N=69**
	Dizziness/Lightheadedness, units (SD)	5.1 (2.33)	5.1 (2.04)
	Mean Standing SBP, mmHg (SD)	95.7 (20.09)	94.7 (21.53)

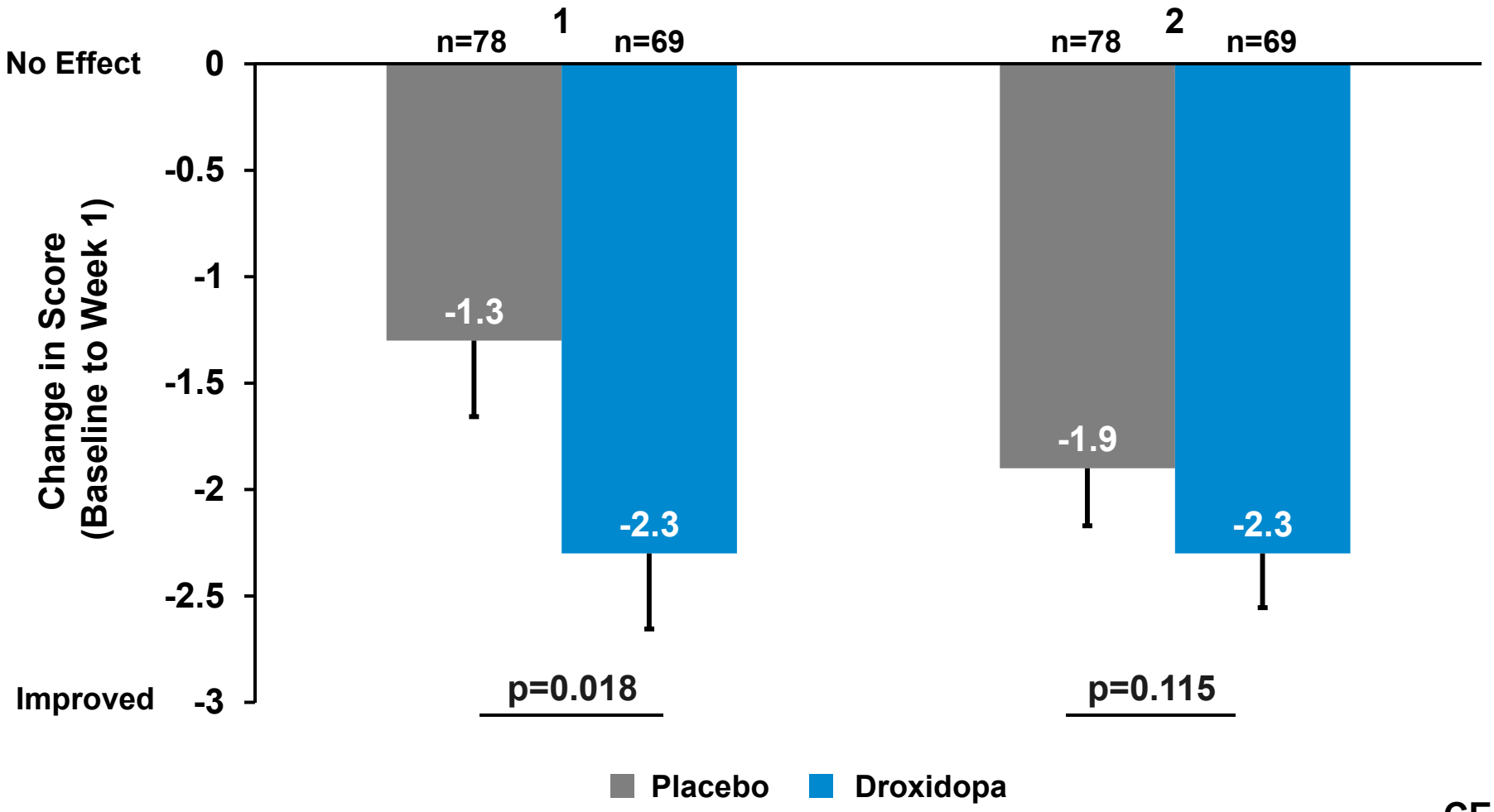
Study 306B:
Concomitant Medications

	Randomized-Controlled Phase	
	Placebo (N=82) n (%)	**Droxidopa (N=89) n (%)**
Any Concomitant Medication	**82 (100.0)**	**89 (100.0)**
Sinemet	65 (79.3)	70 (78.7)
Monoamine Oxidase B Inhibitors	31 (37.8)	35 (39.3)
Dopamine Agonists	24 (29.3)	31 (34.8)
Fludrocortisone	16 (19.5)	30 (33.7)
Selective Serotonin Reuptake Inhibitors	21 (25.6)	30 (33.7)
Proton Pump Inhibitors	22 (26.8)	23 (25.8)
COMT Inhibitors	19 (23.2)	19 (21.3)
Anticholinesterases	11 (13.4)	18 (20.2)
HMG CoA Reductase Inhibitors	23 (28.0)	18 (20.2)
Clonazepam	12 (14.6)	15 (16.9)
Thyroid Hormones	10 (12.2)	14 (15.7)
Systemic Anti-Infectives	19 (23.2)	12 (13.5)

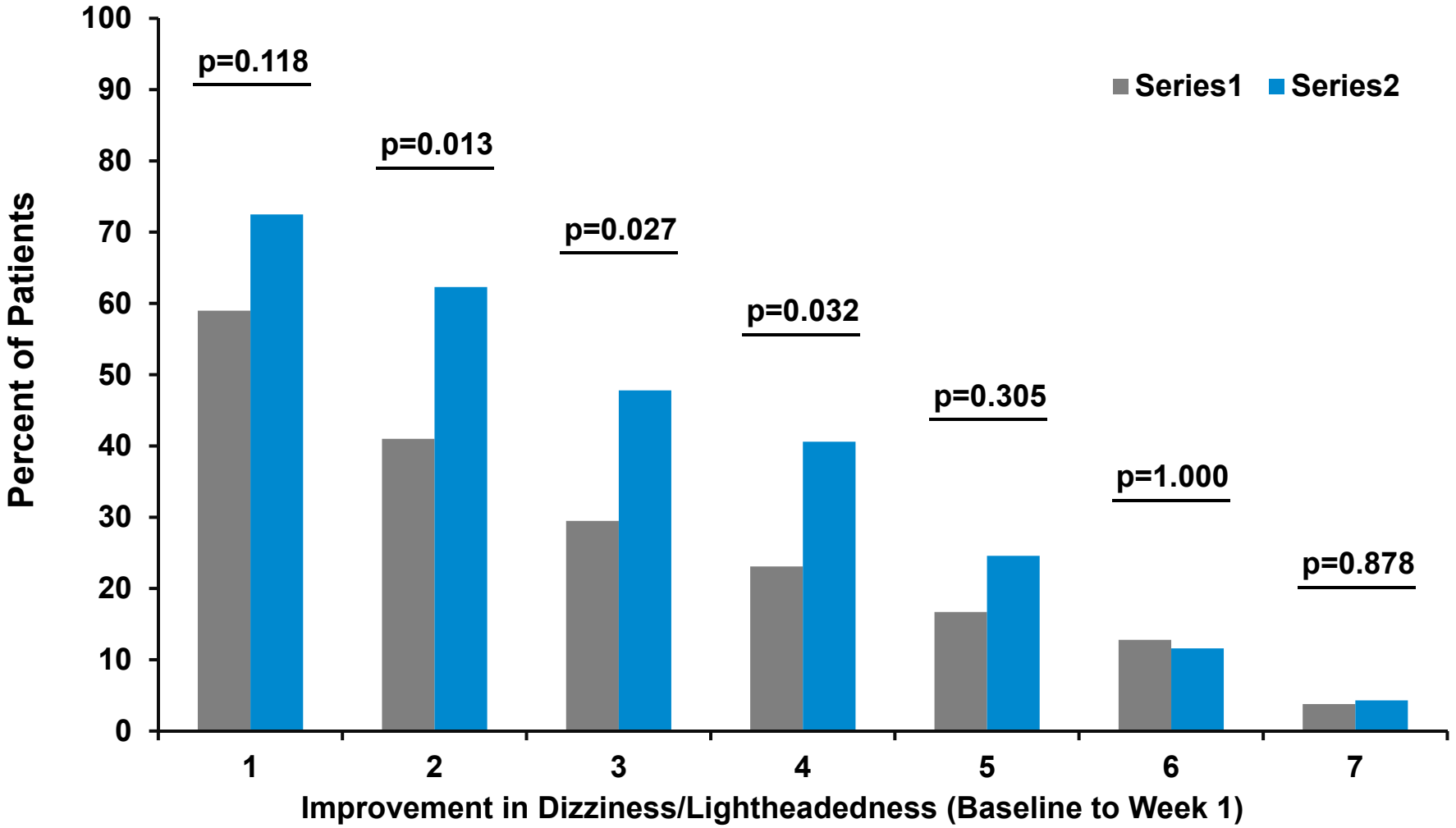
Study 306B, Week 1:
Dizziness/Lightheadedness



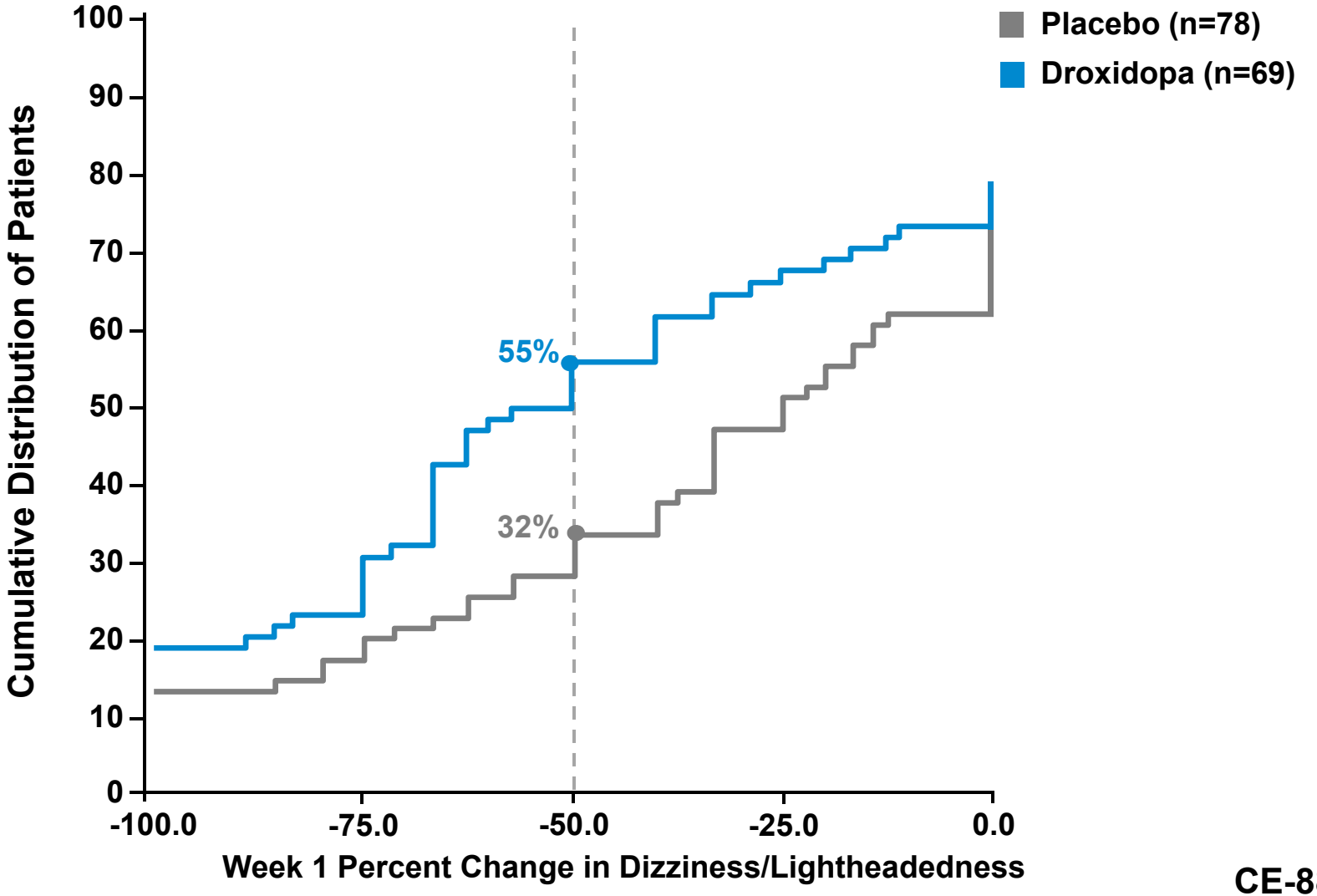
Study 306B, Week 1:
Dizziness/Lightheadedness and OHQ Composite



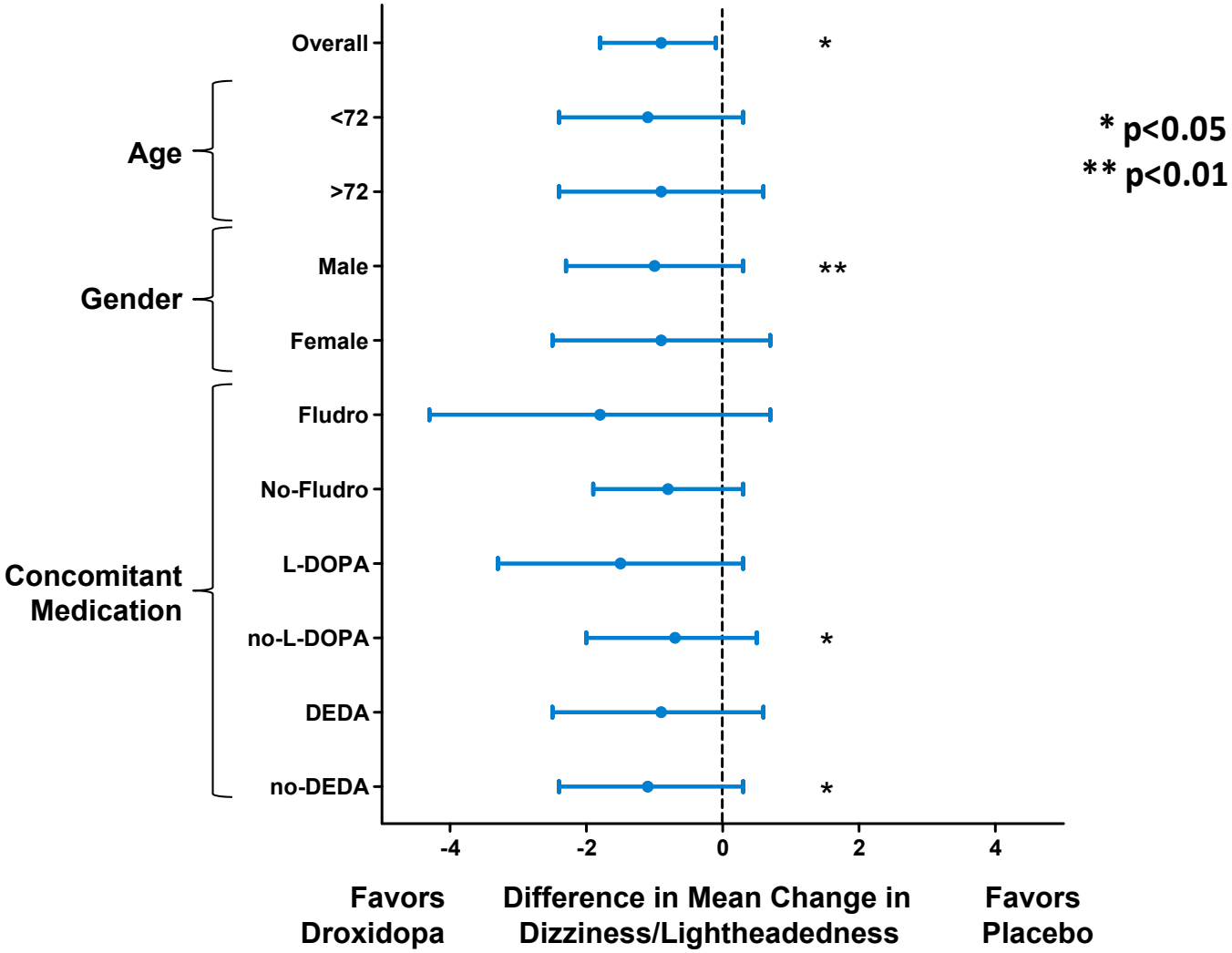
Study 306B, Week 1:
Dizziness/Lightheadedness Response



Study 306B, Week 1: % Improvement
Dizziness/Lightheadedness Response

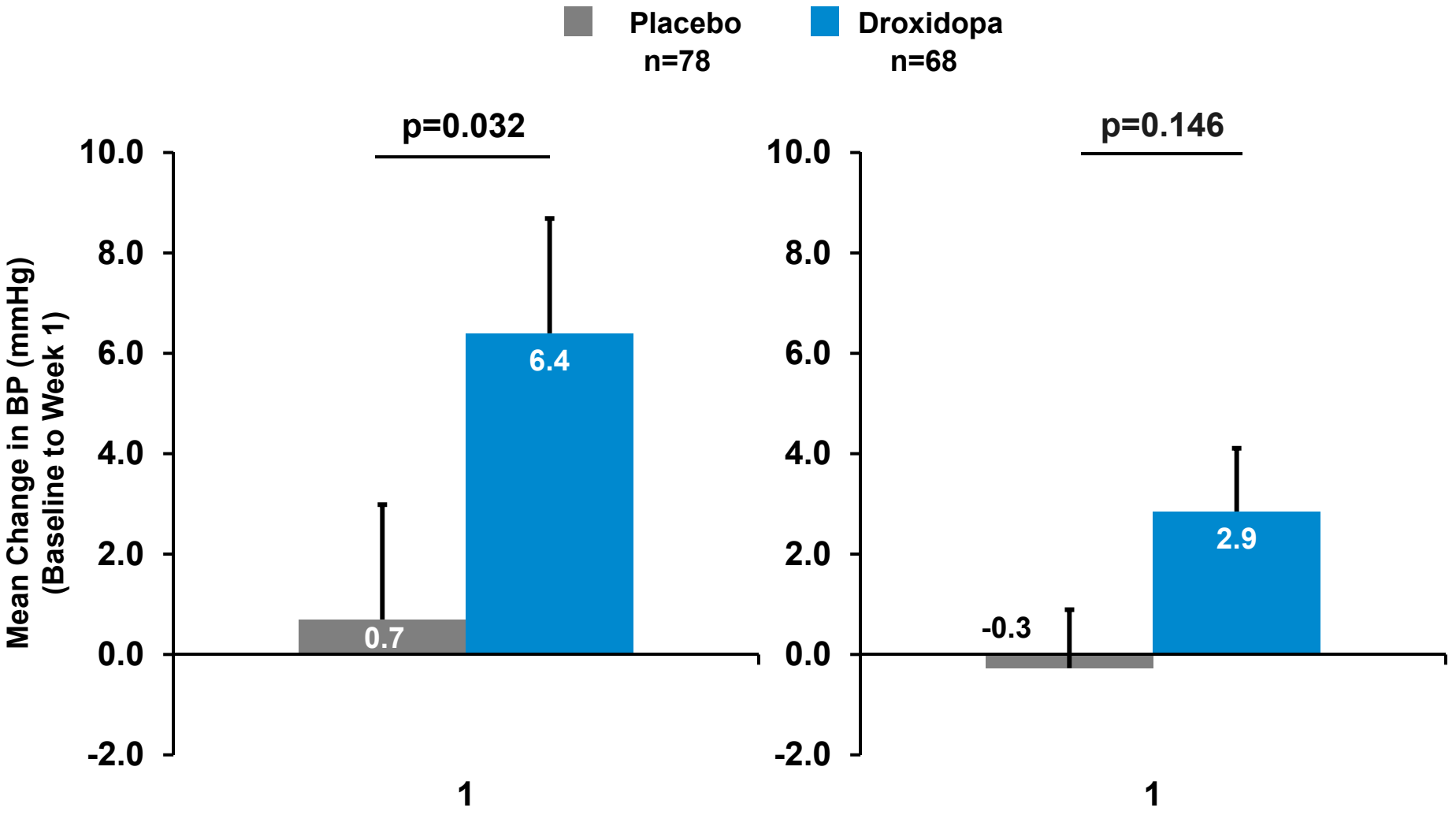


Study 306B, Week 1
Dizziness/Lightheadedness by Subgroups



* p<0.05
** p<0.01

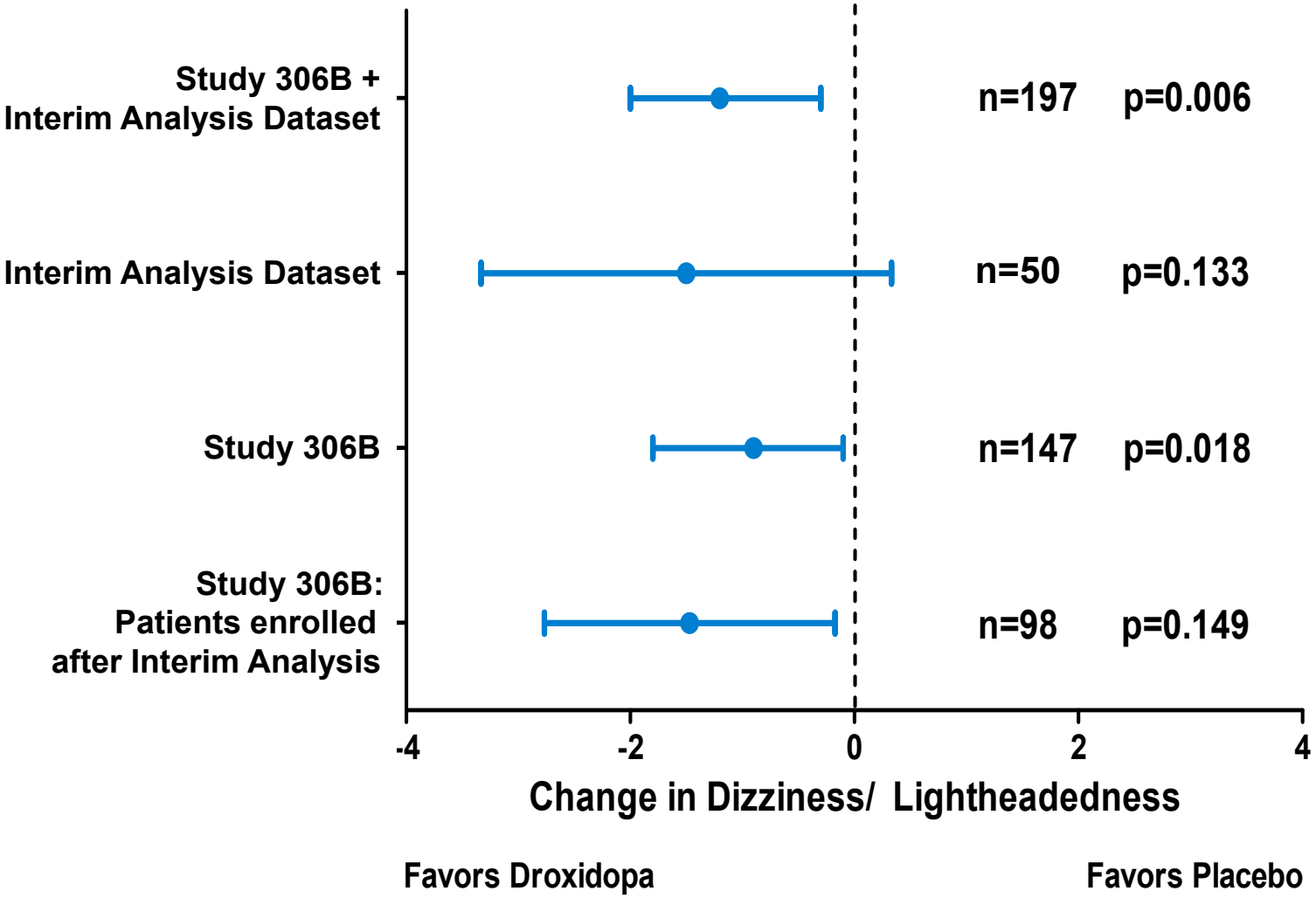
Study 306B, Week 1:
Increases in Standing Blood Pressure



CE-90

Study 306B: Sensitivity Analyses
Blinding

Pre- and Post-Interim Analysis: Dizziness/Lightheadedness

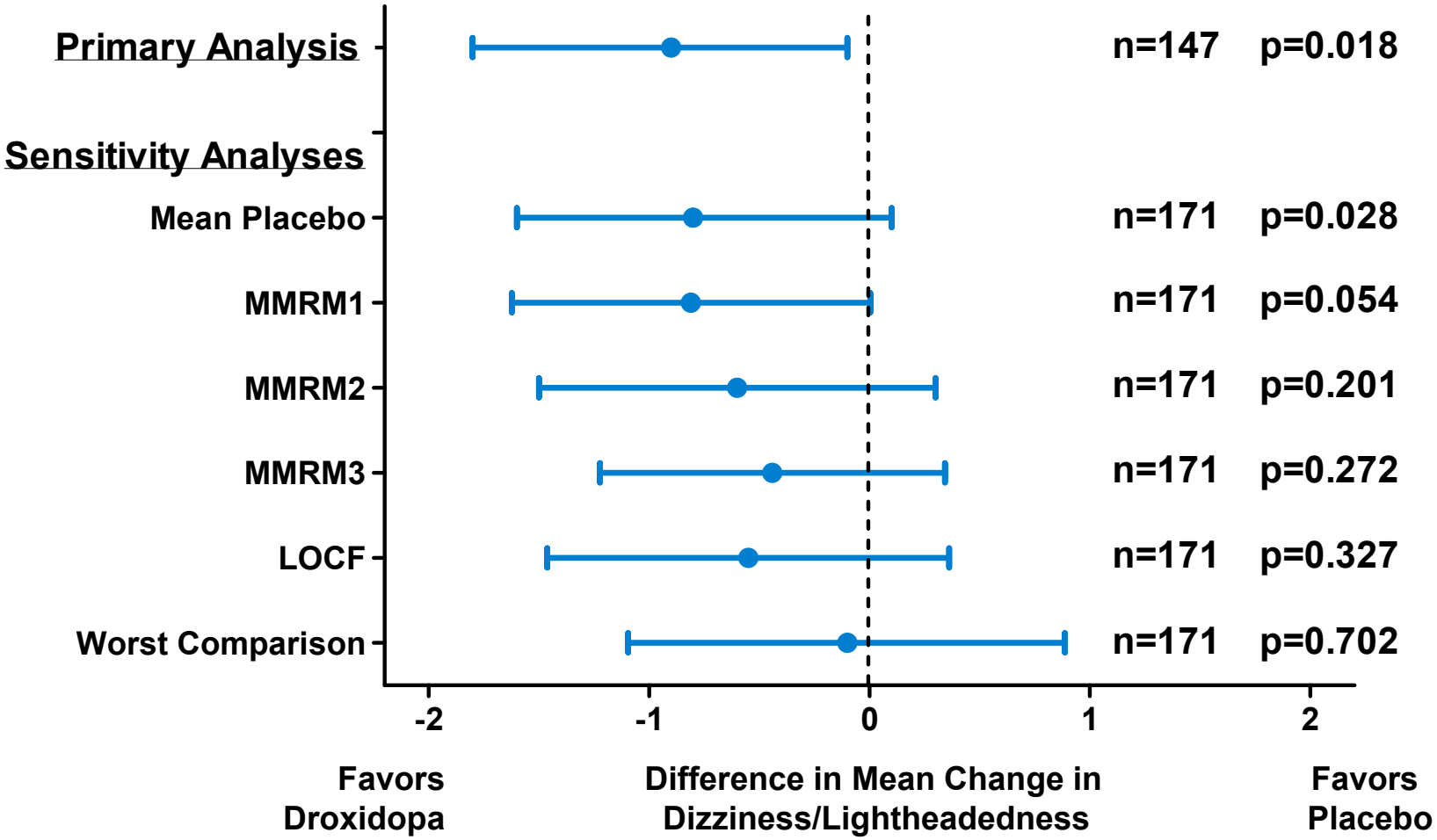


Study 306B: Sensitivity Analyses
Loss to Follow-Up

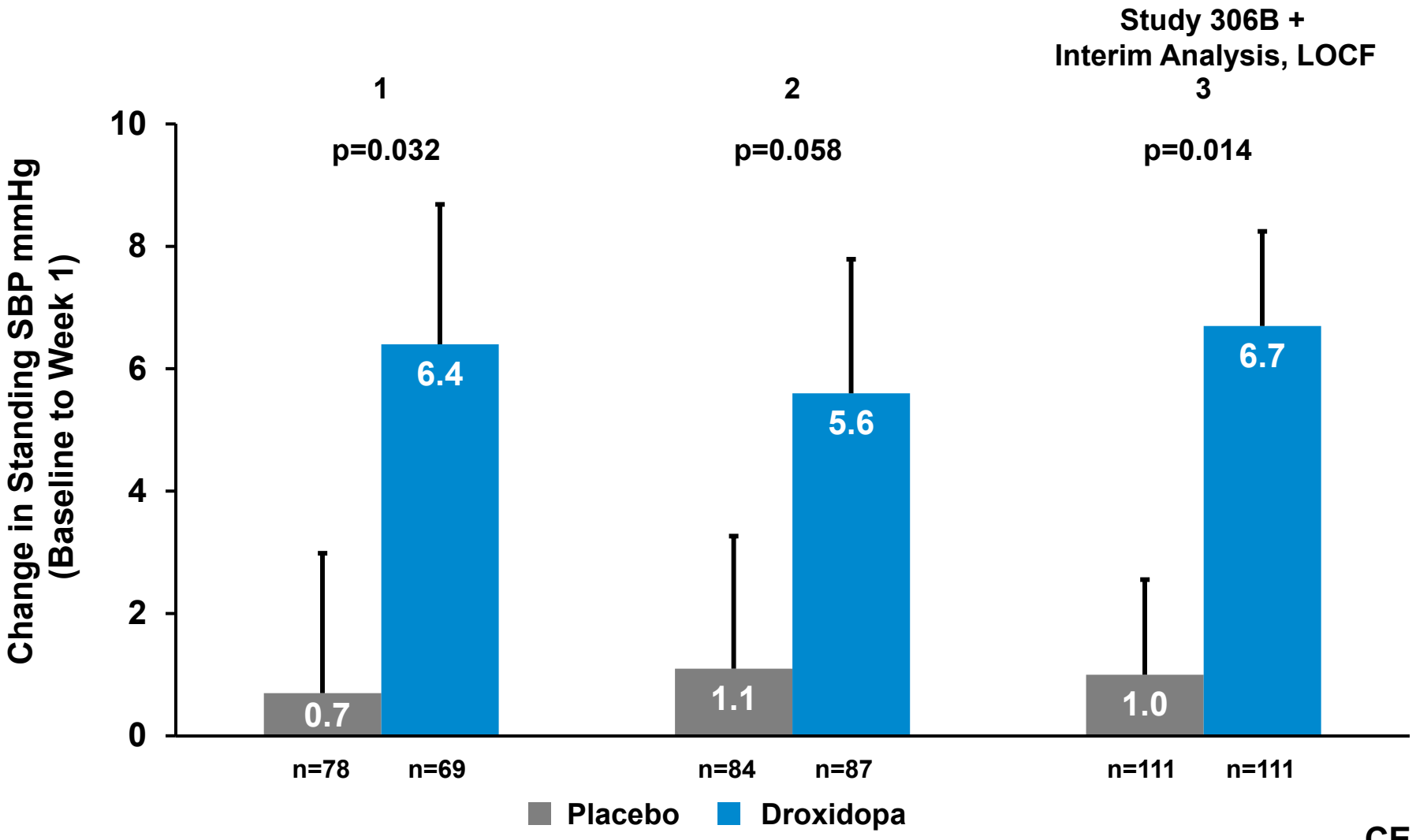
Study 306B:
Loss to Follow-up

Investigator-Determined Reasons	Placebo n (%)	Droxidopa n (%)
Total Dropouts	**6**	**18**
AE or BP Related	4 (66.7)	6 (33.3)
Other	2 (33.3)	3 (16.7)
Lack of Efficacy	0	3 (16.7)
Investigator Decision	0	2 (11.1)
Patient Withdrew Consent	0	2 (11.1)
Treatment Failure	0	1 (5.6)
Protocol Violation	0	1 (5.6)

Study 306B, Week 1:
Imputations for Dizziness (ITT)

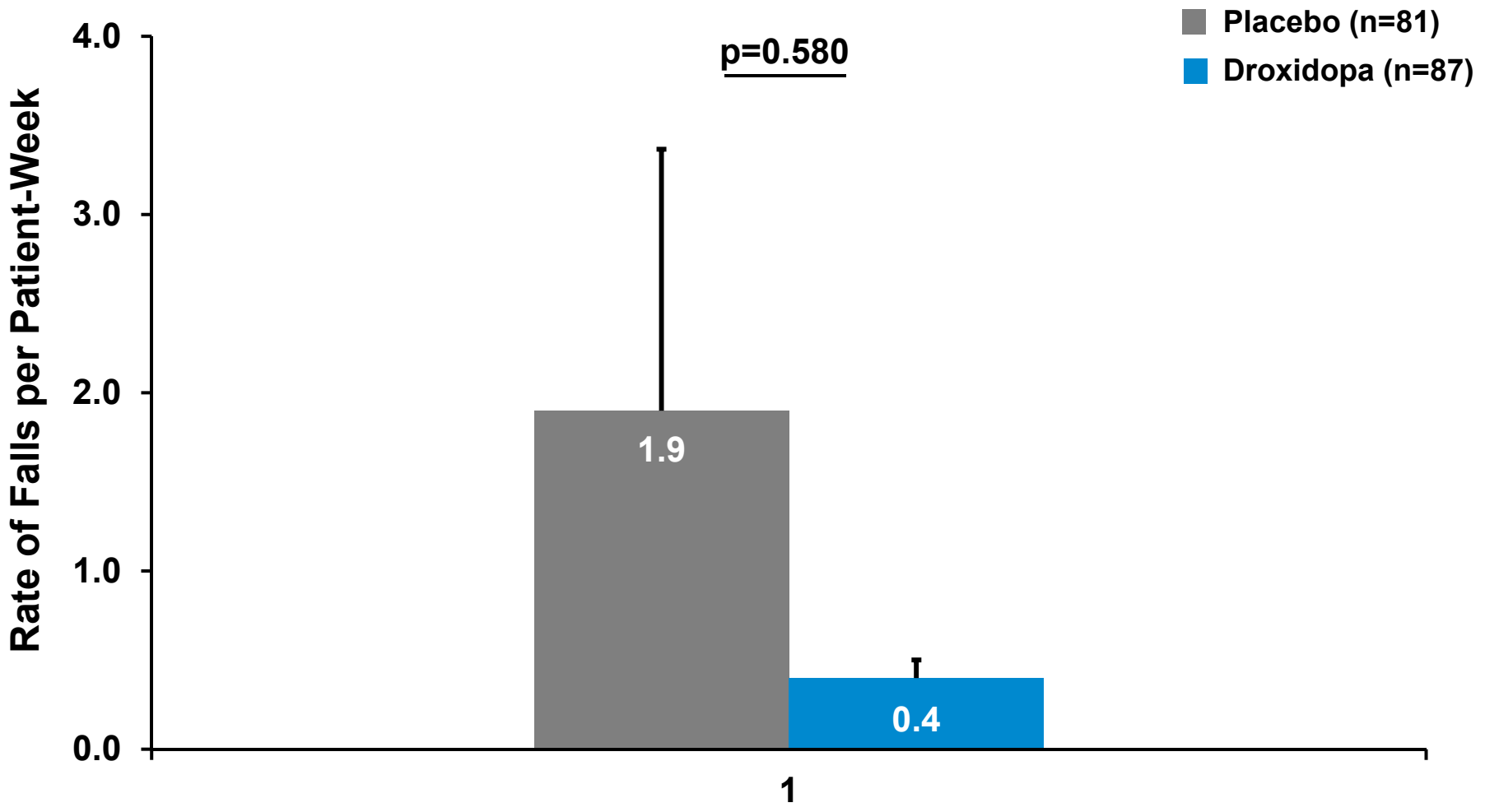


Study 306B, Week 1:
Imputations for Standing SBP



Falls and Fall-Related Injuries

Study 306B:
Mean Rate of Falls Per Patient-Week



CE-98

Study 306B:
Fall-Related Injuries (ITT)

	Placebo (N=82)		Droxidopa (N=89)	
Adverse Event	**n (%)**	**E**	**n (%)**	**E**
Total Number of Patients Reporting AEs	**21 (25.6)**	**35**	**15 (16.9)**	**24**
Excoriations	7 (8.5)	7	5 (5.6)	5
Contusion	10 (12.2)	12	3 (3.4)	4
Skin Laceration	7 (8.5)	7	3 (3.4)	6
Laceration	1 (1.2)	1	2 (2.2)	2
Pain	0	0	2 (2.2)	2
Injury	1 (1.2)	1	1 (1.1)	1
Face Edema	0	0	1 (1.1)	1
Arthralgia	1 (1.2)	1	1 (1.1)	1
Back Pain	1 (1.2)	1	1 (1.1)	1
Conjunctival Hemorrhage	0	0	1 (1.1)	1
Facial Bones Fracture	1 (1.2)	1	0	0
Fall	1 (1.2)	1	0	0
Fibula Fracture	1 (1.2)	1	0	0
Joint Sprain	1 (1.2)	1	0	0
Traumatic Brain Injury	1 (1.2)	1	0	0

Durability

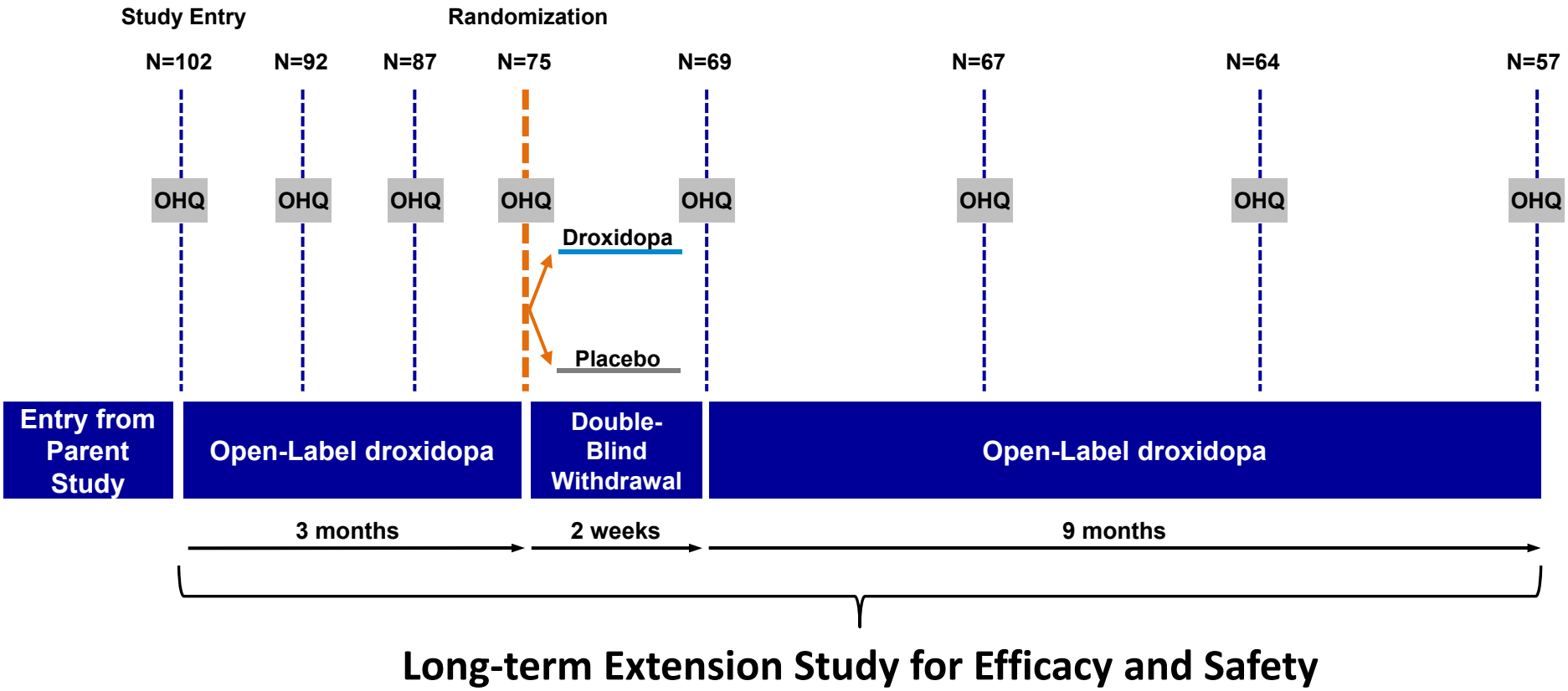
Regulatory Guidance:
Short-Term Benefits Adequate for Approval

"…*the Agency agreed to accept data demonstrating a short-term benefit of midodrine as adequate evidence to support continued approval.*

Therefore, I believe that data strongly demonstrating a short-term clinical benefit (e.g., improvement in symptoms or ability to function) of droxidopa in patients with NOH would be adequate to support approval, with a possible requirement to verify durable clinical benefit postapproval."

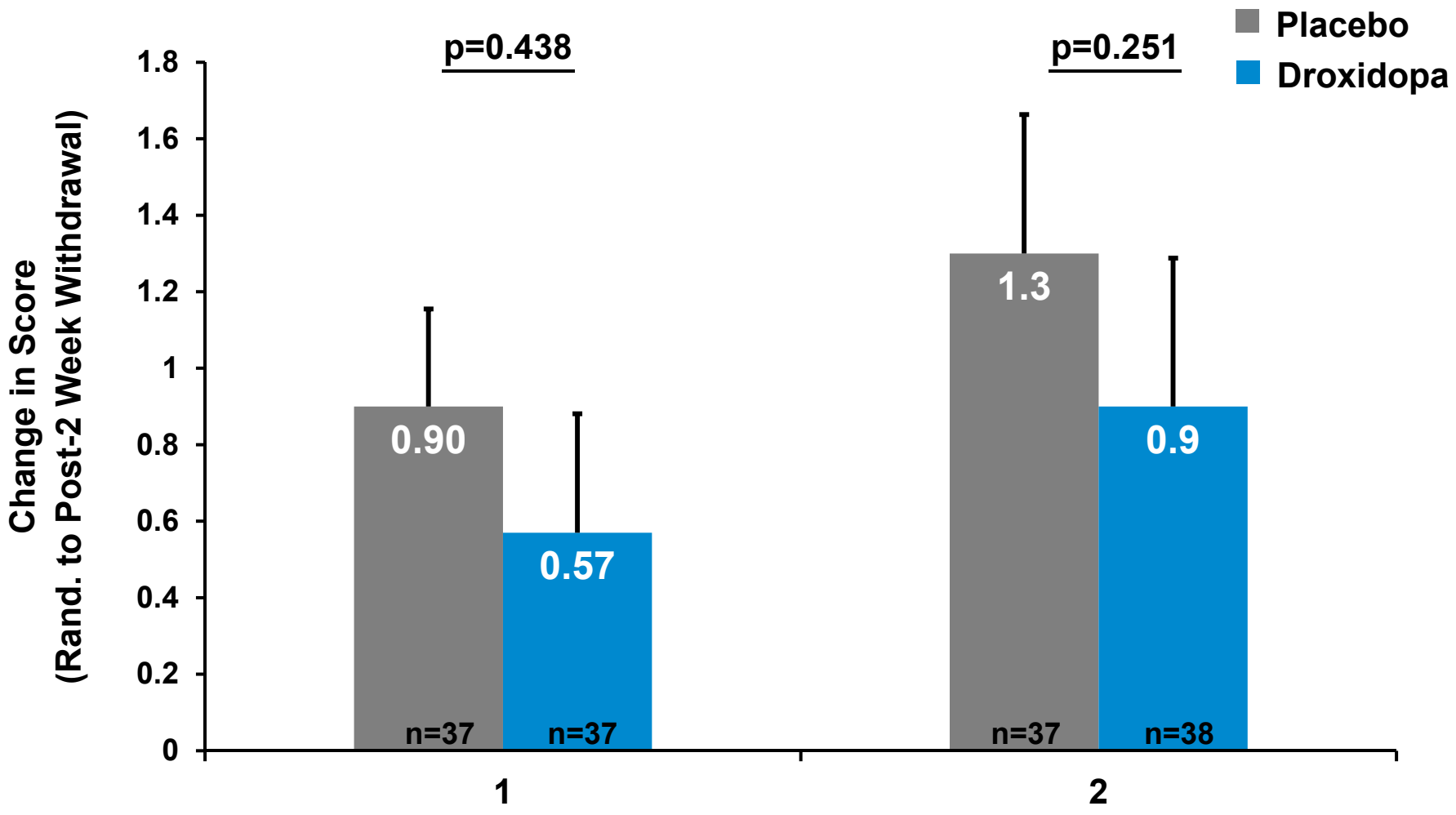
FDA Correspondence, Director, Office of New Drugs; 08 February 2013

Study 303:
Study Design



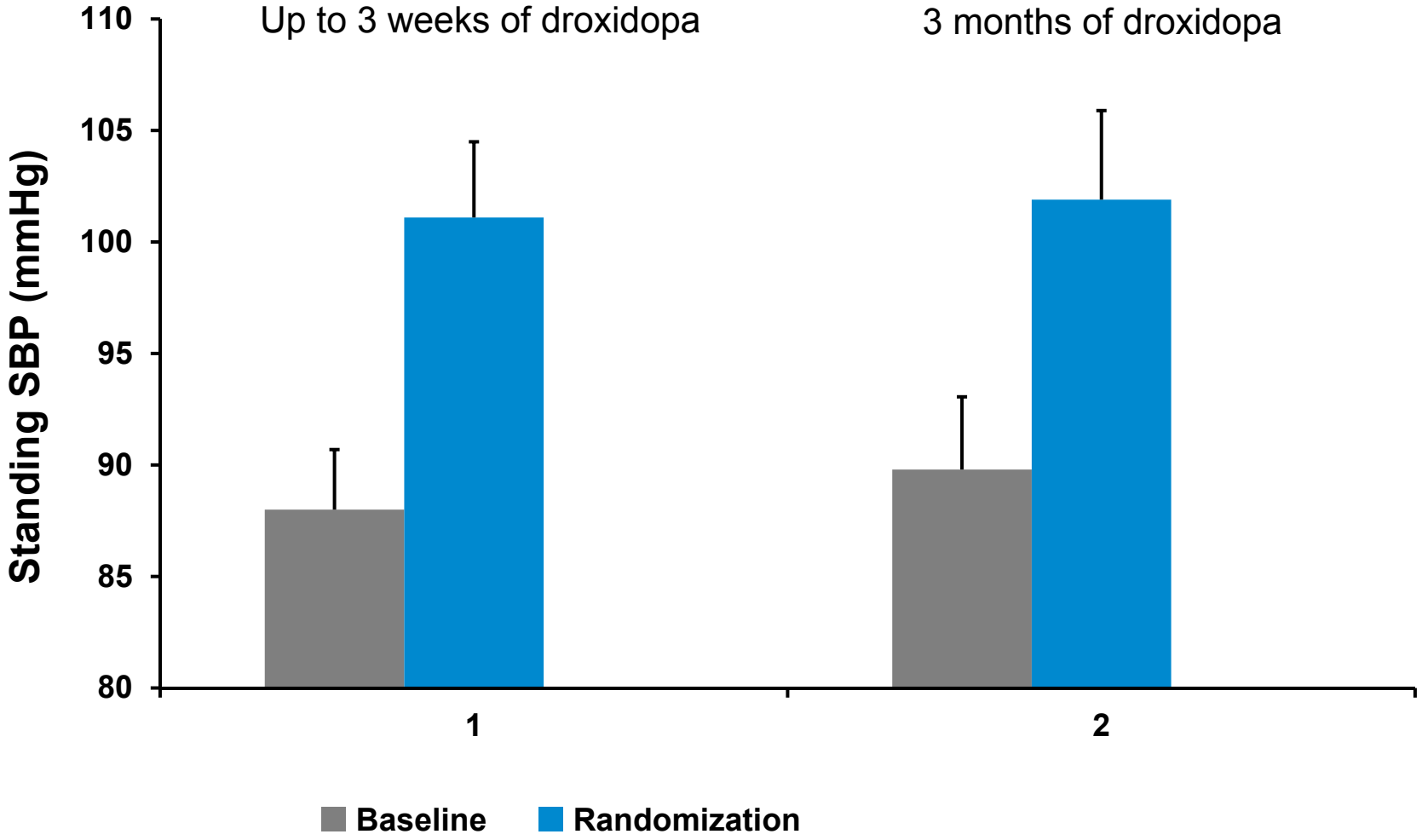
CE-102

Study 303: Primary Analysis
Randomized Withdrawal Phase

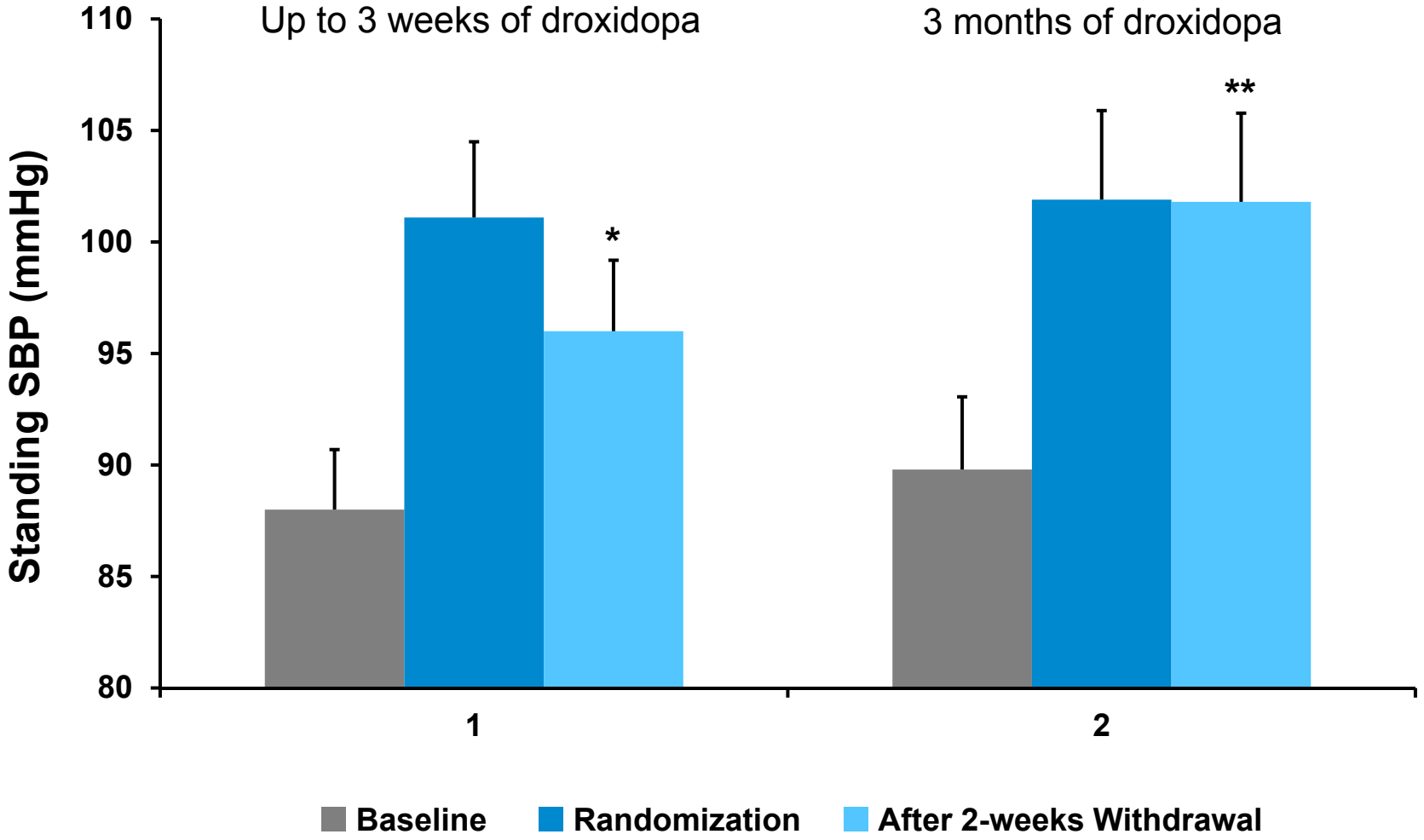


CE-103

Studies 302 and 303:
Potential Carryover Effect

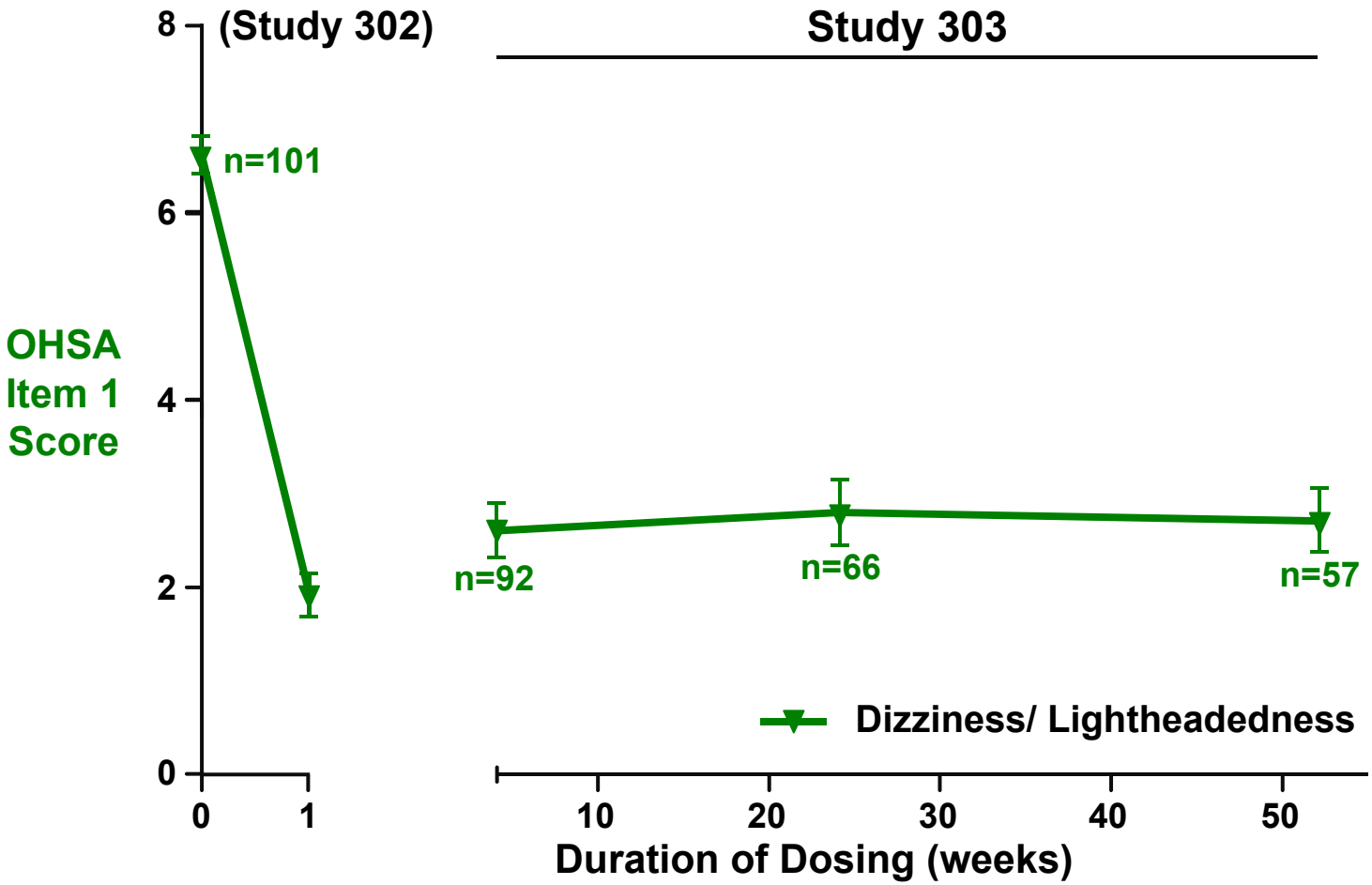


Studies 302 and 303:
Potential Carryover Effect

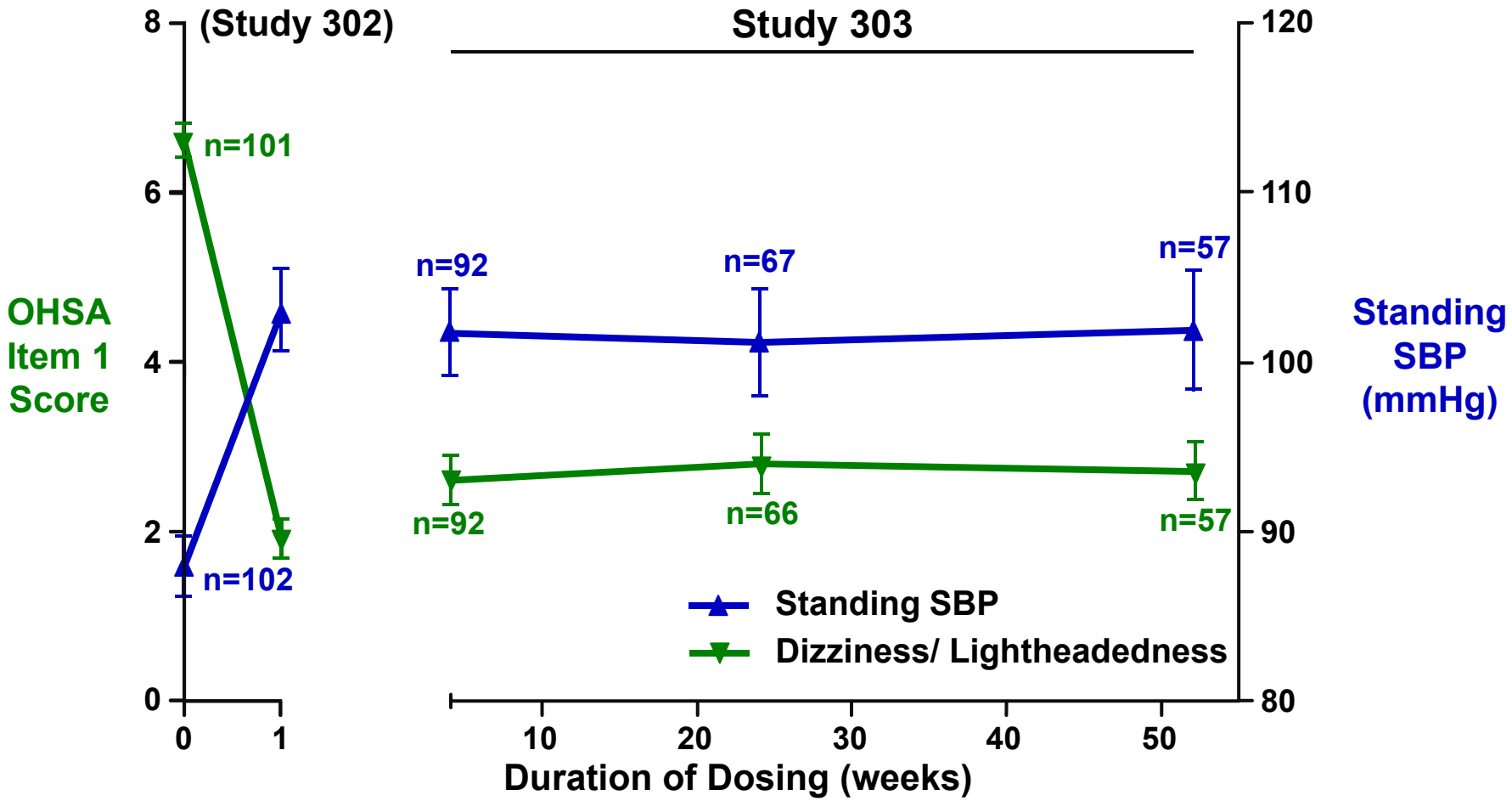


* p=0.011 compared to baseline
** p<0.001 compared to baseline

Study 303:
Long-Term Open-Label Extension

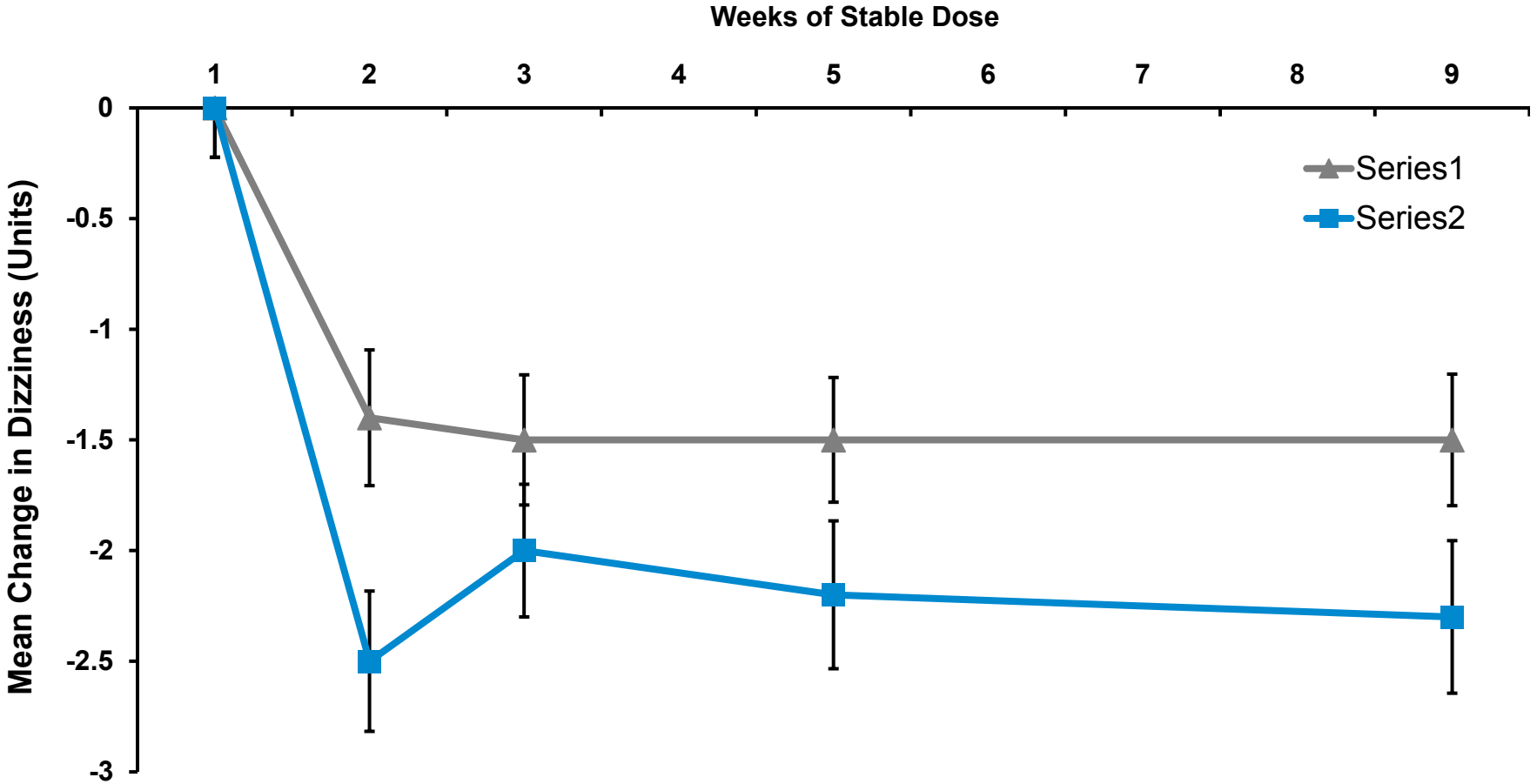


Study 303:
Long-Term Open-Label Extension



CE-107

Study 306B + Interim Analysis Dataset: Durability in Dizziness/Lightheadedness

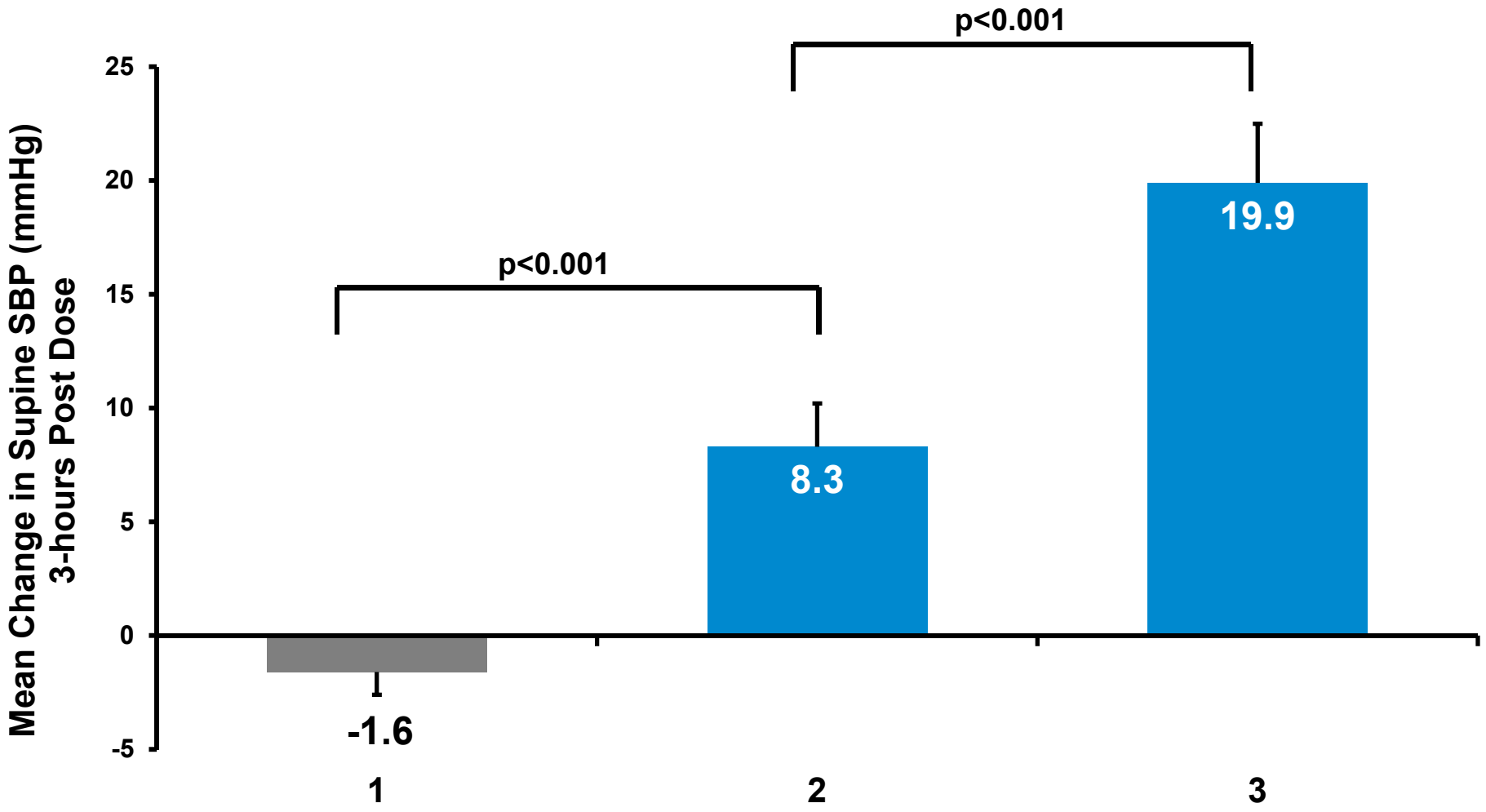


p-value:	**p=0.006**	**p=0.330**	**p=0.120**	**p=0.077**
Placebo:	n=105	n=102	n=98	n=92
Droxidopa:	n=92	n=91	n=89	n=84

CE-108

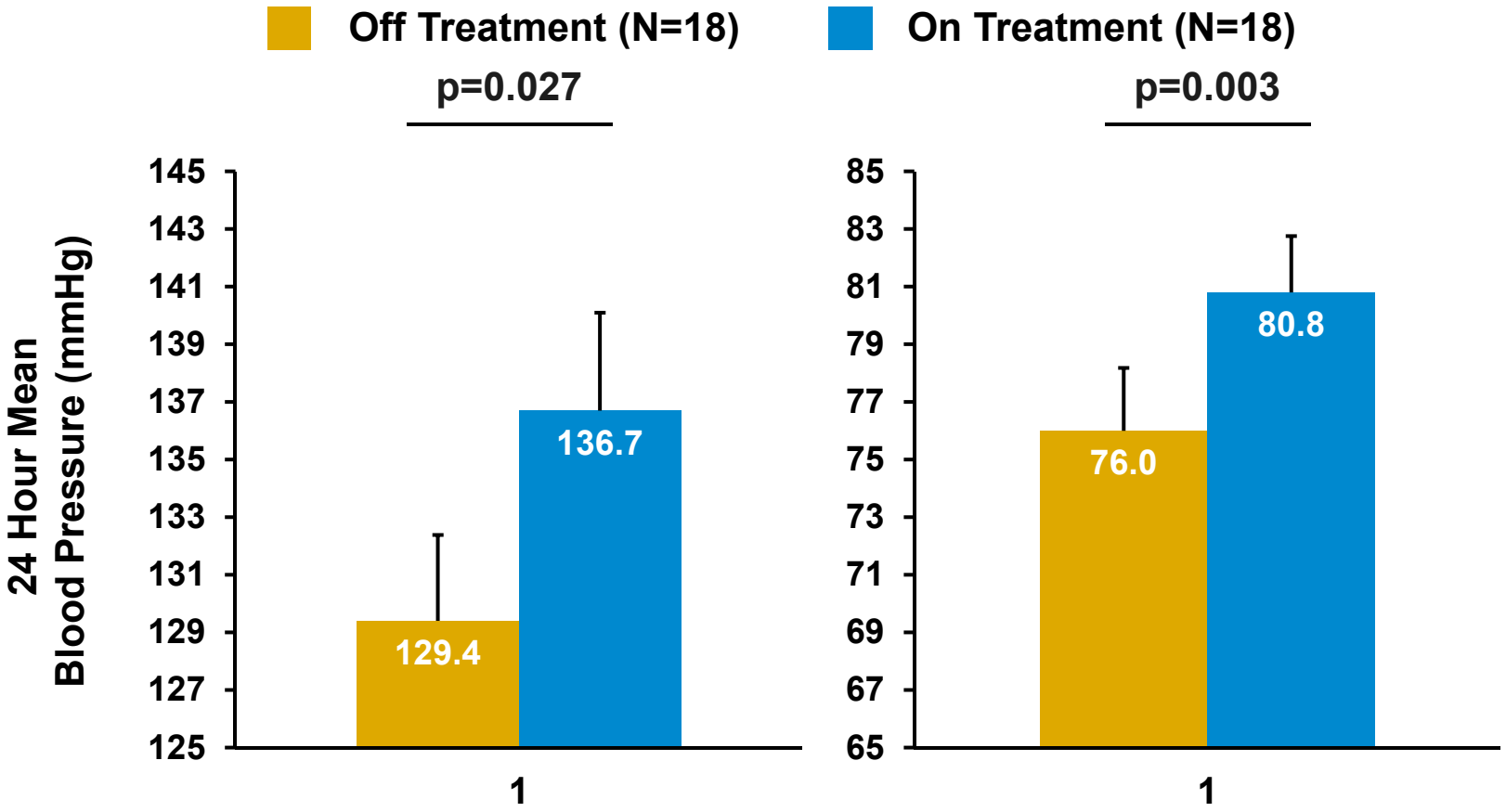
Blood Pressure Studies

Study 102:
Dedicated Thorough QTc Study (N=52)



CE-110

Study 305:
Ambulatory BP Monitoring Study



CE-111

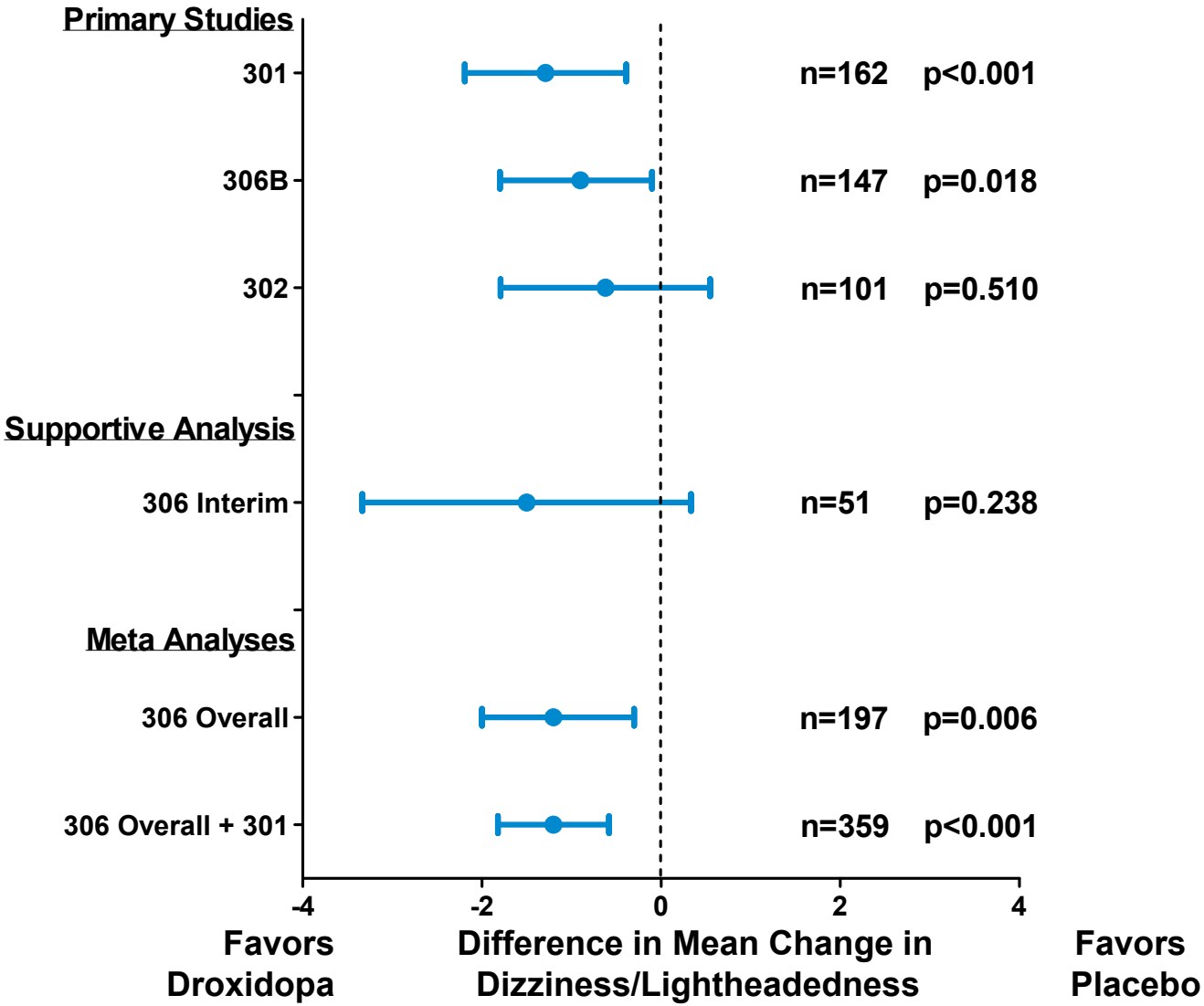
Additional Studies:
Blood Pressure Effect

Study	N	Design	Endpoint	SBP Improvement Post-Droxidopa	p-value
Study 301	162	<2 weeks OL titration	Δ standing SBP Baseline to End of Titration ~3 hours post dose	**23.2 mmHg**	p<0.001
Study 302	101	<2 weeks OL titration	Δ standing SBP Baseline to End of Titration ~3 hours post dose	**24.1 mmHg**	p<0.001
DSP Study S10002	121	28 days DB treatment Placebo v 300mg TID	Δ orthostatic SBP decrease 3 minute tilt	**11.6 mmHg**	p=0.035
Kaufmann 2003[1]	19	DB crossover Following OL dose ranging	Peak standing SBP 3 minutes post-standing 3.5 hours post-dose	**27.0 mmHg**	p<0.001
Mathias 2001[2]	33	10 weeks OL titration and treatment	Δ orthostatic SBP decrease 2 minutes post-standing, Baseline to final visit	**17.7 mmHg**	p=0.007
Freeman 1999[3]	10	Single dose DB crossover Placebo v 1000mg	Peak Δ upright SBP 5 hours post-dose	**27.9 mmHg**	p<0.001

1. Kaufmann et al. *Circulation.* 2003;108:724-72.; data approximated from publication
2. Mathias et al. *Clin Auton Res*. 2001;11(4):235-242.
3. Freeman et al. *Neurology*. 1999;53:2151-7.

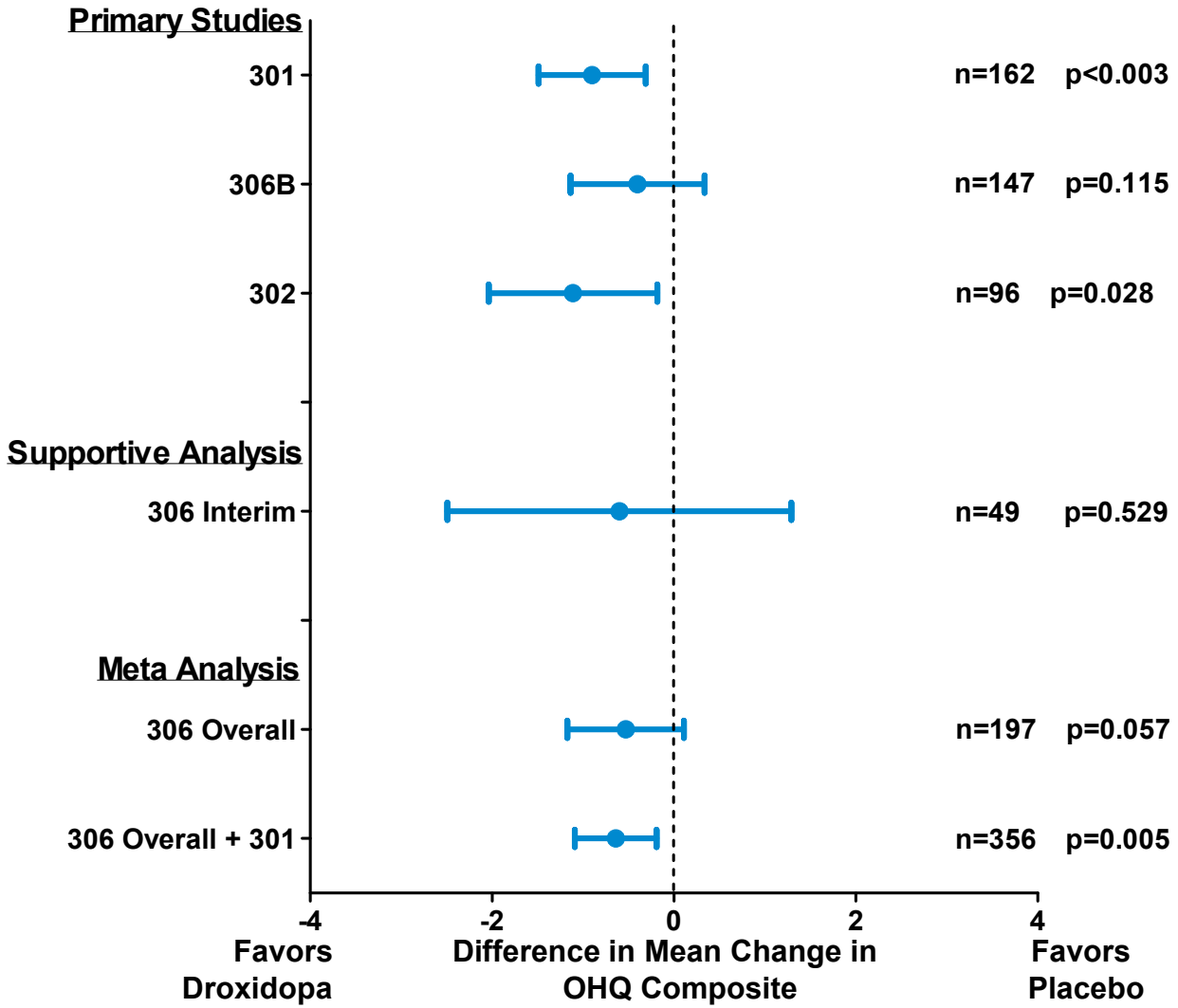
Overall Summary of Efficacy

Dizziness/Lightheadedness



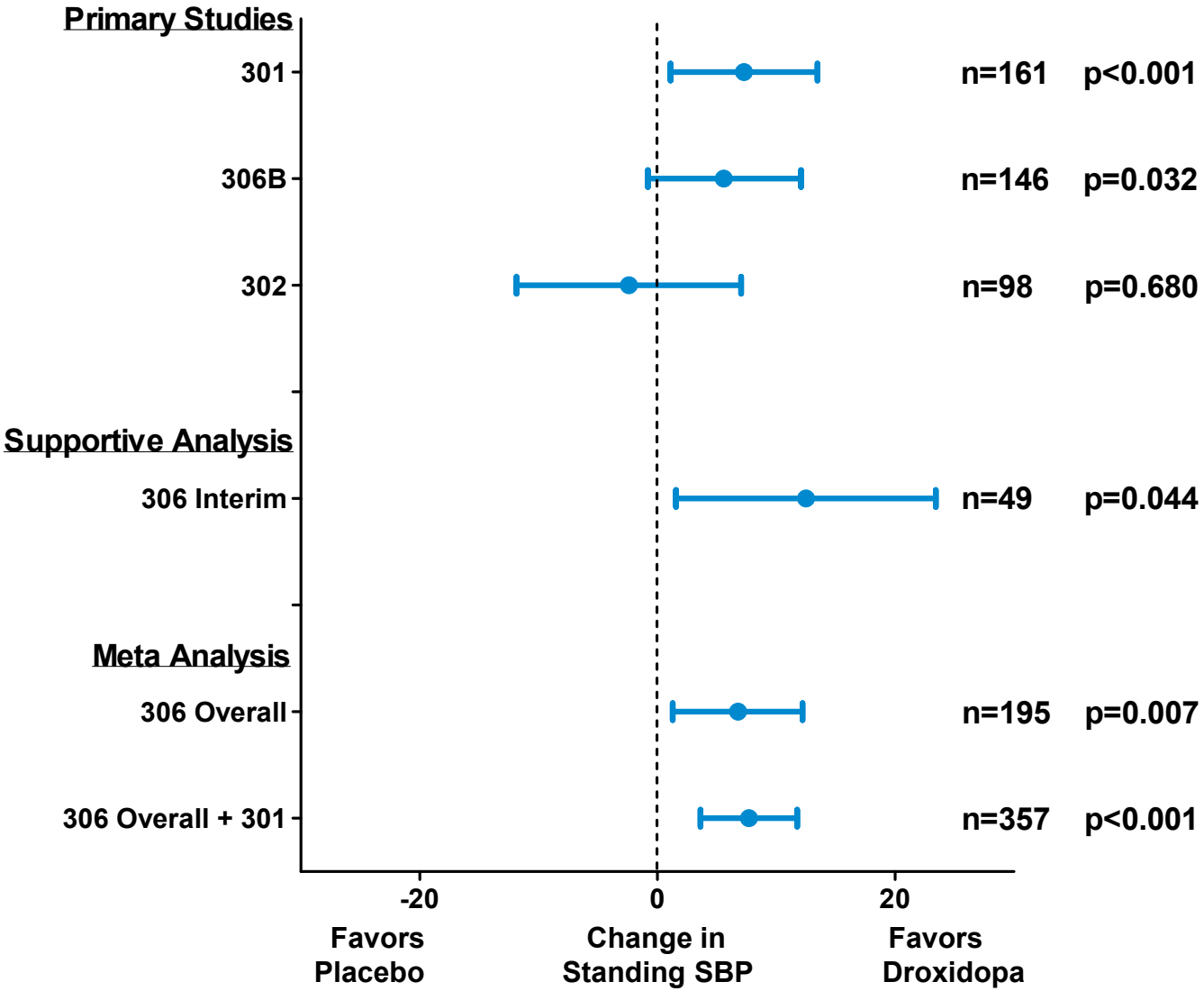
CE-114

OHQ Composite Scores



CE-115

Standing Systolic Blood Pressure



Efficacy Summary:
Substantial Evidence of Short-Term Effectiveness

Two Pivotal Studies

- Study 301 (N=162): conclusively demonstrates short-term clinical benefit
  - Review under a Special Protocol Assessment
  - Primary endpoint, OHQ Composite: p=0.003
  - Dizziness/Lightheadedness: p<0.001
  - Increase in standing SBP: p<0.001

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  - Increase in standing SBP: p<0.001
- Study 306B (N=147): confirms results from Study 301
  - Primary endpoint, Dizziness/Lightheadedness: p=0.018
  - Increase in standing SBP: p=0.032
  - Approx. 80% fewer falls and approx. 34% fewer fall-related injuries

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Supportive Study

- Study 302 (N=101): supportive randomized placebo-controlled trial
  - Primary endpoint failed to demonstrate efficacy
  - Hypothesis generating analysis supports efficacy: OHQ Comp; p=0.026
  - Secondary endpoints: broad range of clinical benefits supports efficacy

Safety Results

Large Safety Database

- 820 patients treated with droxidopa in Chelsea and European clinical studies sponsored by Dainippon Sumitomo Pharma
  - 162 additional patients since original submission
- 8-10 week placebo-controlled safety data
  - Including comparative dose-titration data
- Increased exposure from initial submission to resubmission
  - Long-term study grouping: ~198 to ~435 patient-years

Combined Safety Database:
Exposure by Dose

	Duration of Exposure to Droxidopa			
	<6 Weeks	≥6 Months	≥1 Year	≥2 Years
Total Number of Subjects	**820**	**391**	**263**	**92**
Total Daily Dose				
200 – 300mg	108	35	31	2
400 – 600mg	175	69	47	11
900mg	178	89	52	24
1200mg	155	70	38	15
1500mg	93	47	38	16
1800mg	111	81	57	24

Randomized, Placebo-Controlled Safety Results

Studies 301, 302, and 306:
Deaths – Randomized Phases

- 2 deaths in 666 patients in Chelsea's randomized placebo-controlled trials
- Study 302
  - 58-year-old male MSA patient: During screening (no drug received)
  - 63-year-old female MSA patient: Cardio-pulmonary arrest 11 days post drug discontinuation and after resuming midodrine
- Studies 301 and 306: no deaths

Studies 301, 302 and 306:
Most Common AEs (≥5% Patients)

Adverse Event	Study 301 and 302 1-2 week RCT Phase		Study 306 8-10 week RCT Phase	
	Placebo (N=132) n (%)	Droxidopa (N=131) n (%)	Placebo (N=108) n (%)	Droxidopa (N=114) n (%)
Patients with AEs	**31 (23.5)**	**30 (22.9)**	**87 (80.6)**	**91 (79.8)**
Headache	4 (3.0)	8 (6.1)	8 (7.4)	15 (13.2)
Dizziness	2 (1.5)	5 (3.8)	5 (4.6)	11 (9.6)
Nausea	2 (1.5)	2 (1.5)	5 (4.6)	10 (8.8)
Fatigue	3 (2.3)	2 (1.5)	6 (5.6)	8 (7.0)
Hypertension	0	2 (1.5)	1 (0.9)	8 (7.0)
Contusion	0	0	12 (11.1)	6 (5.3)
Excoriation	1 (0.8)	0	8 (7.4)	6 (5.3)
Skin laceration	0	1 (0.8)	10 (9.3)	5 (4.4)
Edema peripheral	2 (1.5)	0	6 (5.6)	5 (4.4)
Diarrhea	1 (0.8)	1 (0.8)	8 (7.4)	4 (3.5)
Blood pressure increased	0	0	7 (6.5)	4 (3.5)
Back pain	0	0	6 (5.6)	3 (2.6)
Fall	9 (6.8)	1 (0.8)	N/A	N/A

Studies 301, 302 and 306: Serious Adverse Events

Serious Adverse Event	Study 301 and 302 1-2 week RCT Phase		Study 306 8-10 week RCT Phase	
	Placebo (N=132) n (%)	Droxidopa (N=131) n (%)	Placebo (N=108) n (%)	Droxidopa (N=114) n (%)
Patients with SAEs	**1 (0.8)**	**0**	**4 (3.7)**	**5 (4.4)**
Abdominal Pain Upper	0	0	0	1 (0.9)
Atrial Fibrillation	0	0	0	1 (0.9)
Bronchitis Viral	0	0	0	1 (0.9)
Faecaloma	0	0	0	1 (0.9)
Inguinal Hernia	0	0	0	1 (0.9)
Hypertension	0	0	0	1 (0.9)
Mental Status Changes	1 (0.8)	0	0	1 (0.9)
Presyncope	0	0	0	1 (0.9)
Upper Respiratory Tract Infection	0	0	0	1 (0.9)
Syncope	0	0	2 (1.9)	0
Asthenia	0	0	1 (0.9)	0
Fibula Fracture	0	0	1 (0.9)	0
Viral Infection	0	0	1 (0.9)	0
Urinary Tract Infection	1 (0.8)	0	0	0

Studies 301, 302 and 306: AEs Leading to Discontinuation

Adverse Events Leading to Discontinuation	Study 301 and 302 1-2 week RCT Phase		Study 306 8-10 week RCT Phase	
	Placebo (N=132) n (%)	Droxidopa (N=131) n (%)	Placebo (N=108) n (%)	Droxidopa (N=114) n (%)
Patients with AEs	**2 (1.5)**	**0**	**5 (4.6)**	**12 (10.5)**
Hypertension	0	0	1 (0.9)	3 (2.6)
Blood pressure increased	0	0	1 (0.9)	2 (1.8)
Headache	0	0	0	1 (0.9)
Dizziness	0	0	0	1 (0.9)
Parkinson's disease	0	0	0	1 (0.9)
Hypotension	0	0	0	1 (0.9)
Atrial fibrillation	0	0	0	1 (0.9)
Hallucination	0	0	0	1 (0.9)
Mental status changes	0	0	0	1 (0.9)
Abnormal dreams	0	0	0	1 (0.9)
Abdominal discomfort	0	0	0	1 (0.9)
Vision blurred	0	0	0	1 (0.9)
Cholelithiasis	0	0	0	1 (0.9)
Benign neoplasm of bladder	0	0	0	1 (0.9)
Loss of consciousness	1 (0.8)	0	0	0
Syncope	1 (0.8)	0	1 (0.9)	0
Gastroenteritis	0	0	1 (0.9)	0
Malaise	0	0	1 (0.9)	0

Studies 301, 302 and 306:
Adverse Events By Dose

	Study 301 and 302 1-2 week RCT Phase		Study 306 8-10 week RCT Phase	
Dose (TID)	**N**	**Total AEs n (%)**	**N**	**Total AEs n (%)**
Placebo	132	31 (23.5)	108	87 (80.6)
Droxidopa				
100mg	8	2 (25.0)	9	8 (88.9)
200mg	17	5 (29.4)	11	8 (72.7)
300mg	22	5 (22.7)	18	15 (83.3)
400mg	20	2 (10.0)	24	21 (87.5)
500mg	16	6 (37.5)	8	5 (62.5)
600mg	48	10 (20.8)	44	34 (77.3)

Study 306, Titration vs. Treatment
Most Common AEs (>3% droxidopa arm)

	Titration Phase		Treatment Phase	
	Placebo (N=108)	Droxidopa (N=114)	Placebo (N=103)	Droxidopa (N=94)
Adverse Event	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with AEs	**47 (43.5)**	**63 (55.3)**	**68 (66.0)**	**58 (61.7)**
Headache	5 (4.6)	12 (10.5)	3 (2.9)	5 (5.3)
Nausea	5 (4.6)	8 (7.0)	0	2 (2.1)
Dizziness	1 (0.9)	7 (6.1)	4 (3.9)	4 (4.3)
Fatigue	5 (4.6)	7 (6.1)	1 (1.0)	1 (1.1)
Insomnia	1 (0.9)	5 (4.4)	1 (1.0)	0
Hypertension	0	5 (4.4)	1 (1.0)	5 (5.3)
Skin Laceration	4 (3.7)	2 (1.8)	8 (7.8)	4 (4.3)
Blood pressure increased	1 (0.9)	2 (1.8)	6 (5.8)	3 (3.2)
Contusion	2 (1.9)	1 (0.9)	11 (10.7)	5 (5.3)
Excoriation	2 (1.9)	1 (0.9)	6 (5.8)	5 (5.3)
Urinary Tract Infection	0	1 (0.9)	5 (4.9)	3 (3.2)
Edema Peripheral	0	0	4 (3.9)	3 (3.2)
Dehydration	0	0	1 (1.0)	3 (3.2)

Long-Term Safety Results

Long-Term Extension Studies:
Deaths

- 27 deaths across all studies (2 during RCT)
- 25 deaths in 422 patients exposed to droxidopa
  - Causes include: cardiopulmonary arrest, pneumonia, respiratory failure, infection, end-stage disease
  - Causes of death are typical for this population[1,2]
- 11/25 (44.0%) deaths occurred in MSA patients

1. Schrag A et al, *Movement Disorders* 2008; 23: 294-296
2. Pathak et al, *Movement Disorders* 2005 20(9):1213-9

Long-Term Extension Studies:
Summary of Exposure

	Long-Term Studies (N=422)
Duration of Exposure (Days)	
Mean (SD)	376.1 (321.51)
Range	2 - 1389
Average Dose Received (TID)	**n (%)**
100 mg	15 (3.6)
200 mg	57 (13.5)
300 mg	80 (19.0)
400 mg	85 (20.1)
500 mg	72 (17.1)
600 mg	113 (26.8)

Long-Term Extension Studies:
Most Common AEs (≥5% Patients)

Adverse Event	Long-Term Studies (N=422) n	(%)
Total Patients Reporting AEs	**321**	**(76.1)**
Fall	99	(23.5)
Urinary Tract Infection	62	(14.7)
Headache	56	(13.3)
Syncope	53	(12.6)
Dizziness	42	(10.0)
Back Pain	31	(7.3)
Fatigue	30	(7.1)
Nausea	27	(6.4)
Asthenia	27	(6.4)
Constipation	21	(5.0)
Hypertension	*19*	*(4.5)*

Long-Term Extension Studies:
Most Common (≥1% of Patients) SAEs

85% of SAEs considered unlikely or not related to therapy

Most Common SAEs (Fatal and Non-Fatal)	Long-Term Studies (N = 422)	
	n (%)	Events
Total Patients Reporting SAEs	**105 (24.9)**	**224**
Syncope	14 (3.3)	15
Pneumonia	9 (2.1)	12
Dehydration	8 (1.9)	8
Hip fracture	6 (1.4)	8
Urinary tract infection	5 (1.2)	5
Fall	5 (1.2)	5

Long-Term Extension Studies:
AEs Leading to Discontinuation (>1 Patient)

Adverse Event	Long-Term Studies (N=422) n	(%)
Total Patients with AEs Leading to Discontinuation	**63**	**(14.9)**
Pneumonia	3	(0.7)
Respiratory Failure	3	(0.7)
Acute Respiratory Failure	2	(0.5)
Cardio-respiratory Arrest	2	(0.5)
Fall	2	(0.5)
Hallucination	2	(0.5)
Hypertension	2	(0.5)
Hypertensive Crisis	2	(0.5)
Orthostatic Hypotension	2	(0.5)
Myocardial Infarction	2	(0.5)
Transient Ischemic Attack	2	(0.5)
Suicide Attempt	2	(0.5)

Danippon Sumitomo Pharma Post-Marketing Safety

- Estimated total exposure: ~1 million patient-years
  - ~40,000 patients/year receive droxidopa in Japan
- Post-marketing survey and voluntary reports (1989-1999)
  - 1856 patients surveyed; 502 patients received >1 year of treatment
  - No specific adverse reactions attributed to long-term use of droxidopa

Overall Safety Summary

- Short-term randomized studies
  - Low incidence of AEs, mostly mild to moderate in severity
  - Most common: headache, dizziness, nausea
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  - Number and type of AEs generally consistent with randomized controlled studies

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  - Rates of SAEs and AEs consistent with the overall population, most considered unrelated
  - Number and type of AEs generally consistent with randomized controlled studies
- Dainippon Sumitomo studies and post-marketing
  - Low incidence of SAEs and AEs

Agenda

Introduction	**William D. Schwieterman, MD** *Chief Medical Officer* *Chelsea Therapeutics*
Unmet Medical Need	**Roy Freeman, MD** *Professor of Neurology* *Harvard Medical School* *Director, Center for Autonomic and Peripheral Nerve Disorders* *Beth Israel Deaconess Medical Center*
Efficacy and Safety Results	**William D. Schwieterman, MD** *Chief Medical Officer* *Chelsea Therapeutics*
Cardiovascular Safety; **Overall Benefit/ Risk**	**William B. White, MD** *Professor of Medicine and Chief* *Division of Hypertension and Clinical Pharmacology; Cardiology Center* *University of Connecticut Health Center*

Morbidity and Mortality in Patients with Neurogenic Orthostatic Hypotension (nOH)

William B. White, M.D.
Calhoun Cardiology Center
University of Connecticut Health Center, Farmington

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Assessment of the Safety and Benefits of Droxidopa for Patients with nOH

- Characterization of the mortality and CV morbidity of the patient population
- Review of cardiovascular morbidity and deaths
- Clinical and ambulatory blood pressure on droxidopa – a dual-edged assessment process
- Clinical perspectives on the benefits and risks of droxidopa in nOH

Clinical Outcomes in nOH Patients

- Untoward outcomes in nOH include:
  - Development of or exacerbation of supine hypertension
  - Increases in cardiovascular events including syncope/falls, other cardiac morbidities, and death
  - Marked increases in mortality due to infections, respiratory failure, progression of the neurodegenerative process

Mathias CJ and Kimber JR. *Annual Review of Medicine* 1999; 50: 317-336.
Schmidt C et al. *Movement Disorders* 2009; 24: 2136-2142.
Schrag A et al. *Movement Disorders* 2008; 23: 294-296.
Tada M et al. *Archives of Neurology* 2007; 64: 256-260.

Nocturnal Hypertension is a Common Problem in nOH Patient Populations

Parameter	MSA (n=25) %	PSP (n=25) %	PD (n=23) %	Control (n=26) %
Blood Pressure Declines at Night				
Nocturnal SBP fall (vs daytime)	-1.2	-8.6	-8.1	-18.5
Nocturnal DBP fall (vs daytime)	-5.0	-10.4	-9.9	-21.6
Percent of Patients				
Patients with reduced BP fall at night	68	40	48	8
Patients with reversed circadian BP	48	8	22	4
Patients with supine hypertension	60	36	48	12

PSP: Progressive supranuclear palsy

Schmidt C et al. *Movement Disorders* 2009; 24: 2136-2142.

Patients with nOH Associated with MSA Have Poor Prognoses (3 Separate Cohorts)

- Median survival (n=100 patients)[1]
  - 8.6 years for men
  - 7.3 years for women
    (57% of deaths due to respiratory disease/pneumonia)
- Median times from disease onset (n=49 patients) to event[2]
  - Becoming wheel-chair bound: 3.5 years
  - Becoming bedridden: 5.0 years
  - Death: 7.0 years
- 10 of 45 (22%) patients had a fatal event during 5 years of observation
  - 7/10 on respiratory assist devices[3]
- 11 of 141 (8%) of patients died in 6 months; risk greater in Parkinsonian phenotype and those with bladder dysfunction[4]

[1]Schrag A et al. *Movement Disorders* 2008; 23: 294-296.
[2]Tada M et al. *Archives of Neurology* 2007; 64: 256-260.
[3]Shimohata T et al. *J Neurol* 2008; 255: 1483-1485.
[4]Wenning G et al. Lancet 2013; 12: 264-275

Mortality in nOH Patients (n=31) During a Year of Observation was 16%

- 5 of 31 (16.1%) patients with autonomic failure died in the year between observation periods
- No deaths observed in age-matched PD patients without autonomic failure (n=26)

Cause of Death	Neurologic Diagnosis	Demographics
Stroke	PD	78 years old, male
Myocardial infarction	MSA	68 years old, male
Aspiration pneumonia	PD	83 years old, male
Sudden Death	LBD	79 years old, male
Sudden Death	LBD	77 years old, female

LBD – Lewy body disease
Note: Patients were treated with heptaminol (7), midodrine (11), fludrocortisone (6), midodrine + fludrocortisone (7)

Pathak et al, *Mov Disord* 2005 Sep; 20(9):1213-9

Cardiovascular Safety Assessment of Droxidopa

Cardiac Conduction and Heart Rate Were Not Affected by Droxidopa

- In **Studies 301, 302, 303**, **and 306** no effects were observed on QTc or heart rate in nOH patients following droxidopa 100-600 mg TID
- In **Study 102,** no effect of droxidopa on conduction parameters following 600 and 2000 mg in a thorough QT study - 52 healthy volunteers:

Study 102 (mean Δ from baseline)	**Placebo**	**600 mg Droxidopa**	**2000 mg Droxidopa**	**400 mg Moxifloxacin**
Heart Rate (bpm)	0.0	-1.3	-1.5	1.1
PR (ms)	-0.3	0.4	0.7	-1.6
QRS (ms)	0.0	-0.1	-0.5	-0.3
QTcF (ms)	-3.1	-2.8	-2.6	6.1
QTcB (ms)	-3.1	-4.2	-4.2	7.4

Cardiovascular Disorders in Droxidopa Patients at Baseline (Studies 301, 302, and 306)

Cardiovascular Diagnoses at Study Entry	Total (N=666) n (%)
Patients with Cardiovascular Disorders	**307 (46.1)**
Arrhythmias	235 (35.3)
Coronary Artery Disease	164 (24.6)
Valvular Heart Disease	47 (7.1)
Hypertension	113 (17.0)
Ventricular Hypertrophy/Cardiomyopathy	10 (1.5)
Heart Failure	4 (0.6)

Evaluation of Deaths

- Studies 301, 302, 303, 304, and 306 include 638 droxidopa treated patients with approximately 450 patient-years of exposure
- 27 deaths in Chelsea Studies (4.2%); 13 of these occurred in patients with MSA
- 20 were non-cardiovascular - sepsis, aspiration pneumonia, and MSA progression
- 7 CV (un-witnessed or sudden deaths, stroke)

Rates of Nonfatal Cardiovascular Serious Events Across All Studies*

Adverse Event Term	Medical Diagnosis, Post Medical Review	n (%)
Arrhythmias	Atrial Fibrillation/Flutter (4) Supraventricular tachycardia (1)	5 (0.8)
Severe or Malignant Hypertension	Severe hypertension, no TOD (1) Severe hypertension with CHF (1)** Moderate Hypertension non-serious AE (1) Severe hypertension with confusion (1) Recurrent severe hypertension (1)	5 (0.8)
Cerebrovascular Events	Nonfatal stroke (3) Transient ischemic attack (2)	5 (0.8)
Coronary Artery Disease	Coronary revascularization	2 (0.3)
Angina Pectoris	Angina, unstable (1) Angina due to recurrent stent stenosis (1)	2 (0.3)
Cardiac Failure	Hospitalized CHF with pneumonia (1) Hospitalized CHF with aortic stenosis (1)**	2 (0.3)

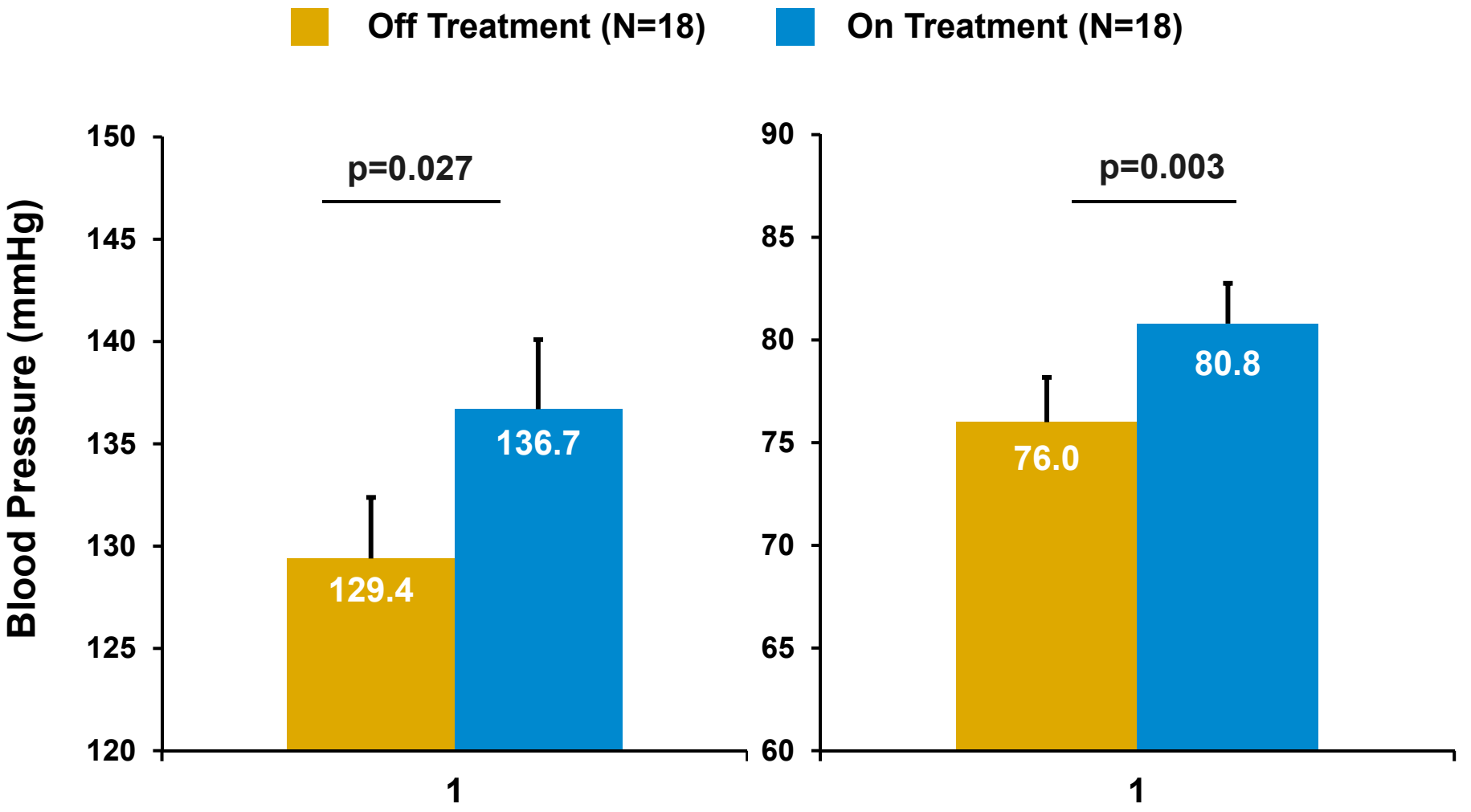
* Studies 102, 301, 302, 303, 304, 305, 306 ; **also on florinef
TOD: target organ damage

Assessment of Blood Pressure

Study 305 Design

- Dedicated 24-hour ambulatory blood pressure monitoring study (N=18)
- Blood pressure measured every 30 minutes
- Measurements taken 1 day off-drug, 1 day on-drug, patients are their own control
- Primary endpoint was change in 24-hour mean blood pressure

Study 305: 24-hour Mean BP Off and On Droxidopa (Mean Dose: 428 mg TID)



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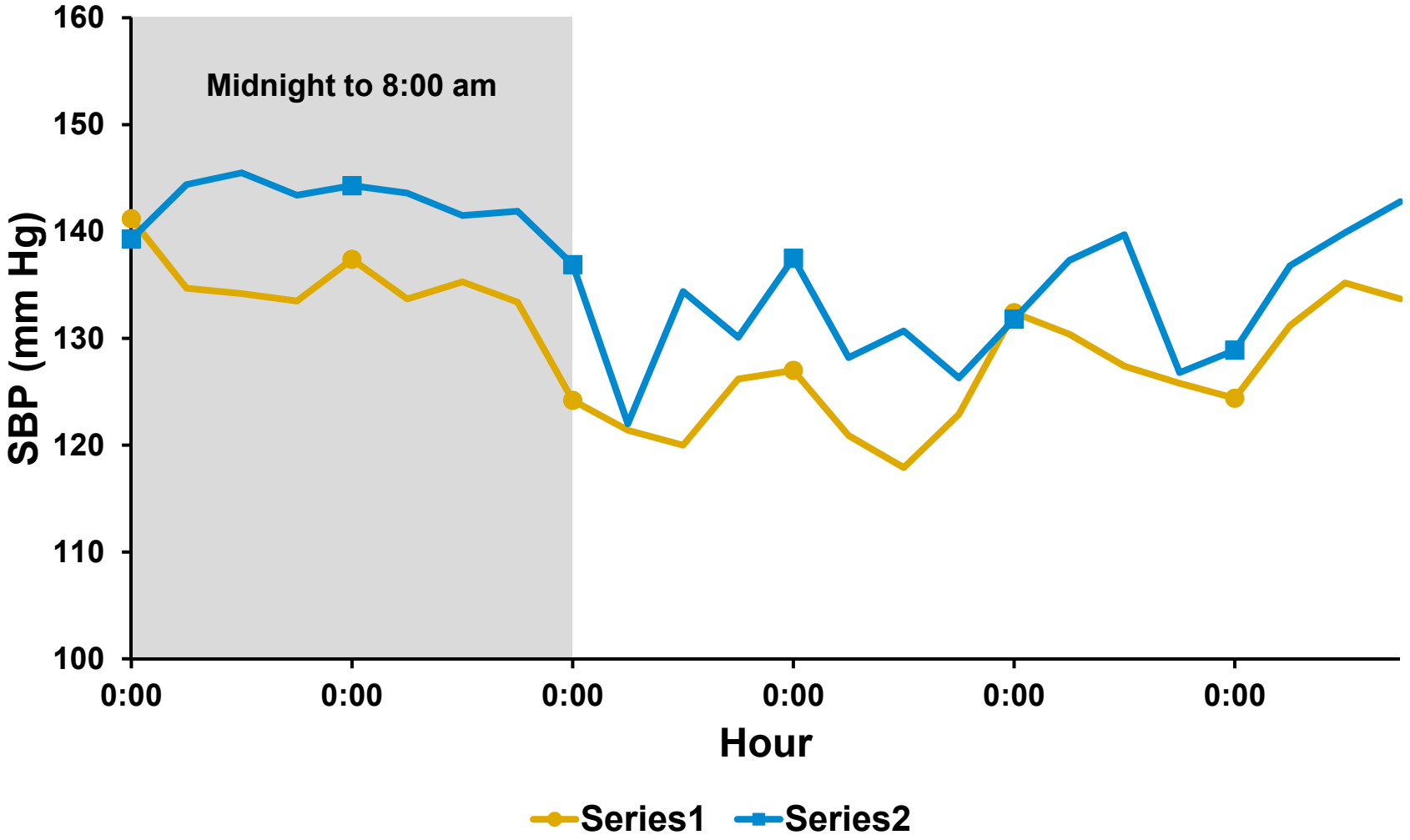
Study 305:
24-hour SBP Profiles Off and On Droxidopa



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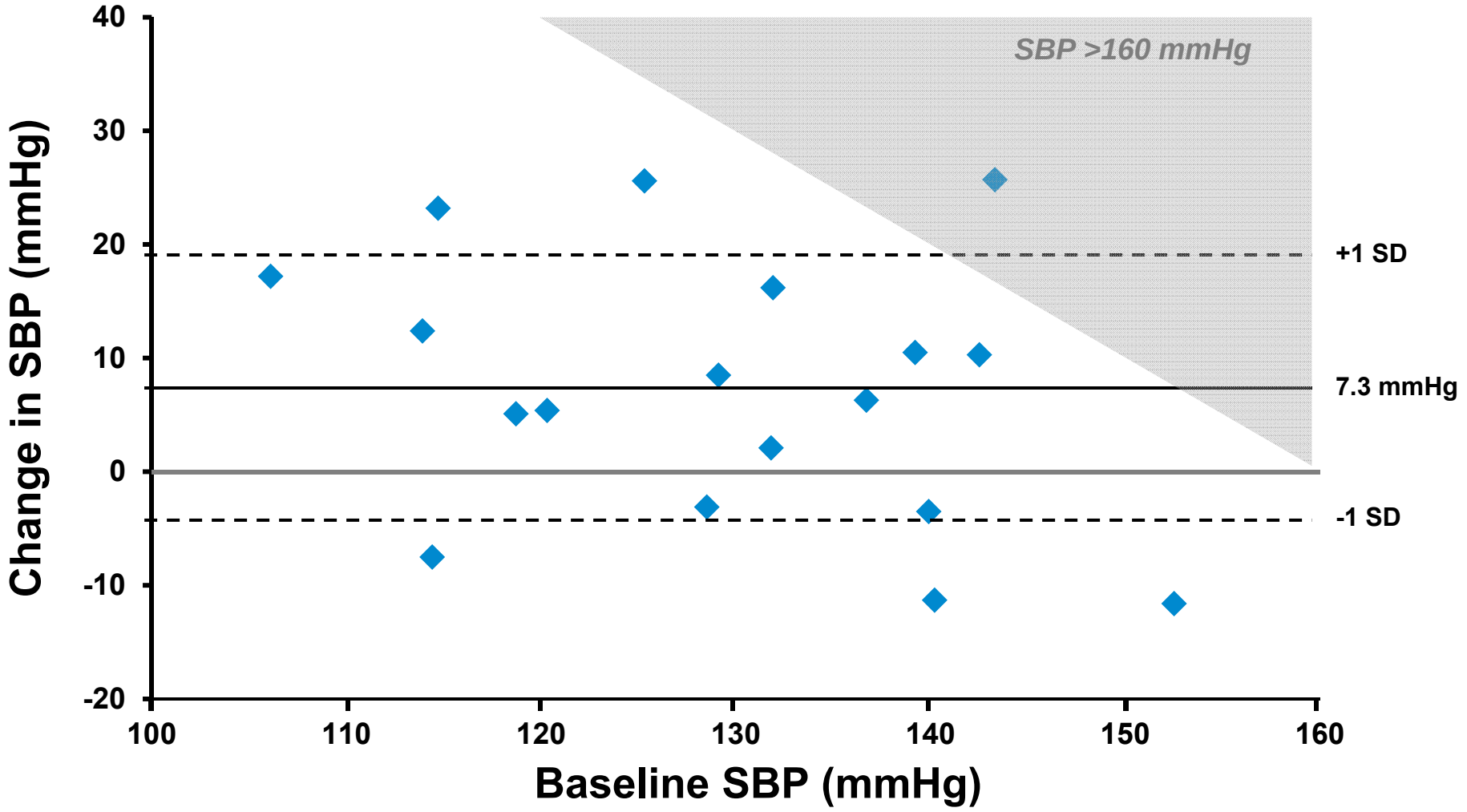
Study 305: Changes in 24-hour SBP According to Baseline SBP (N=18)



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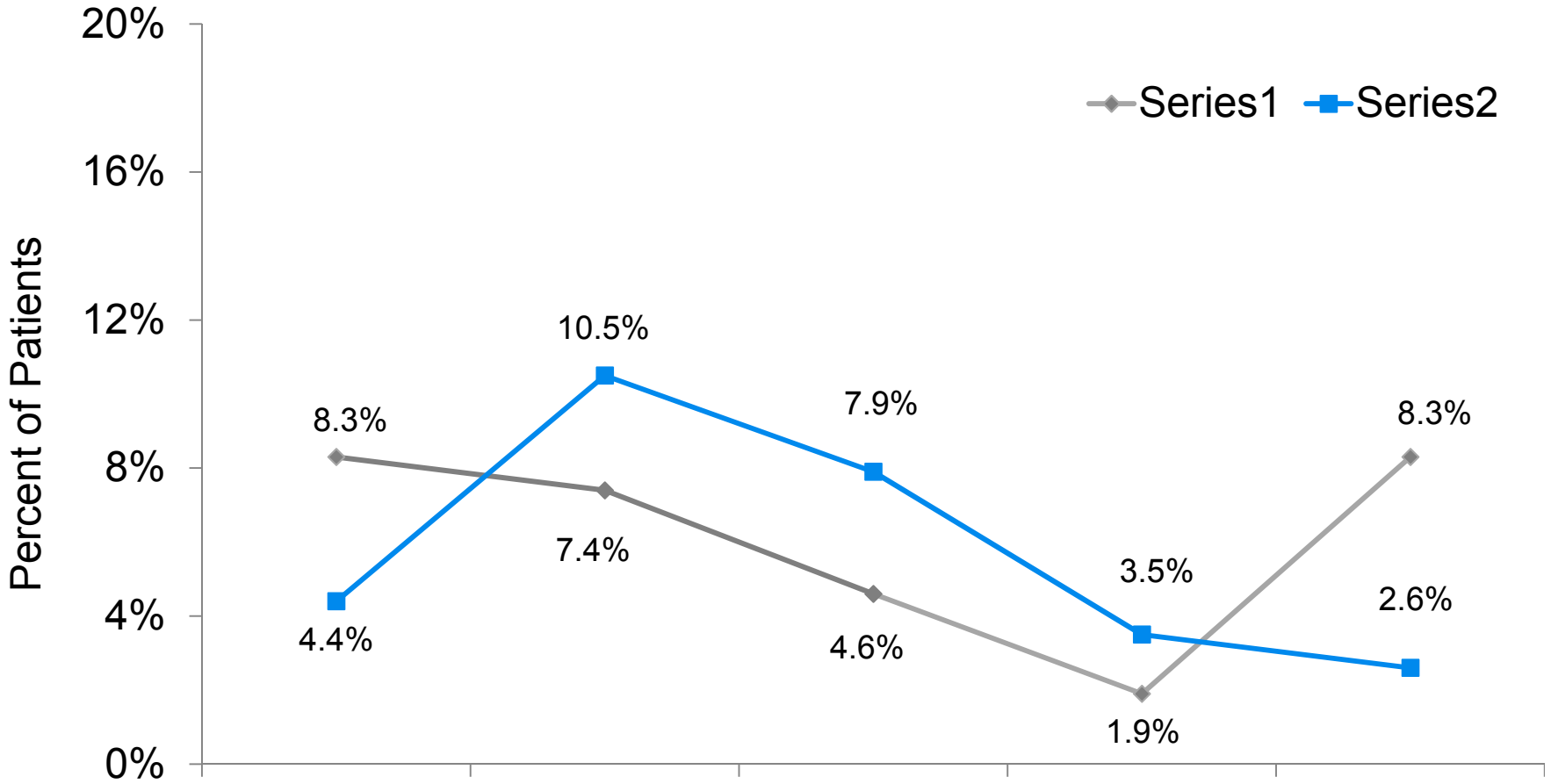
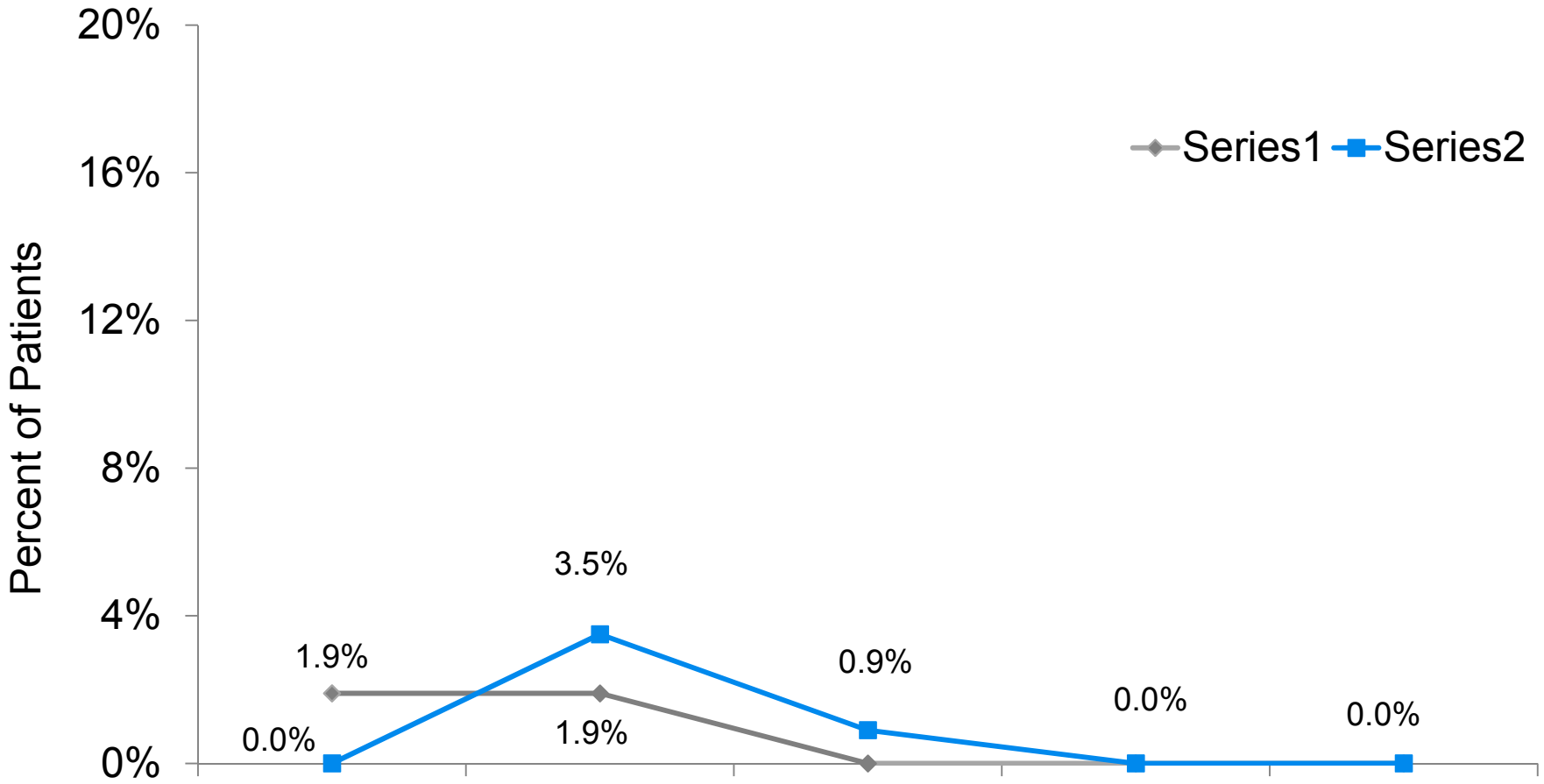
Supine Hypertension (SBP >160mmHg)
Randomized Patients: Overall Study 306



Placebo N=	108	106	101	96	93
Droxidopa N=	114	107	94	90	86

CB-157

Supine Hypertension (SBP >180mmHg)
Randomized Patients: Overall Study 306



Placebo N=	108	106	101	96	93
Droxidopa N=	114	107	94	90	86

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Droxidopa – Clinical Management of Supine Hypertension

- Supine hypertension with droxidopa (>160 mmHg)
  - ~10% of patients
  - More common in those with higher baseline supine BP
  - Initial clinical management includes clinic and home BP monitoring with non-pharmacologic interventions (elevation of head of bed, restrict sodium if appropriate)
- Avoid droxidopa dosing within 4 hours prior to bedtime
  - Physicians and patients can also monitor supine BP as droxidopa dose is up-titrated
  - For more severe BP elevations, droxidopa can be down-titrated or discontinued
  - Short-acting antihypertensive agents can be administered at bedtime if necessary

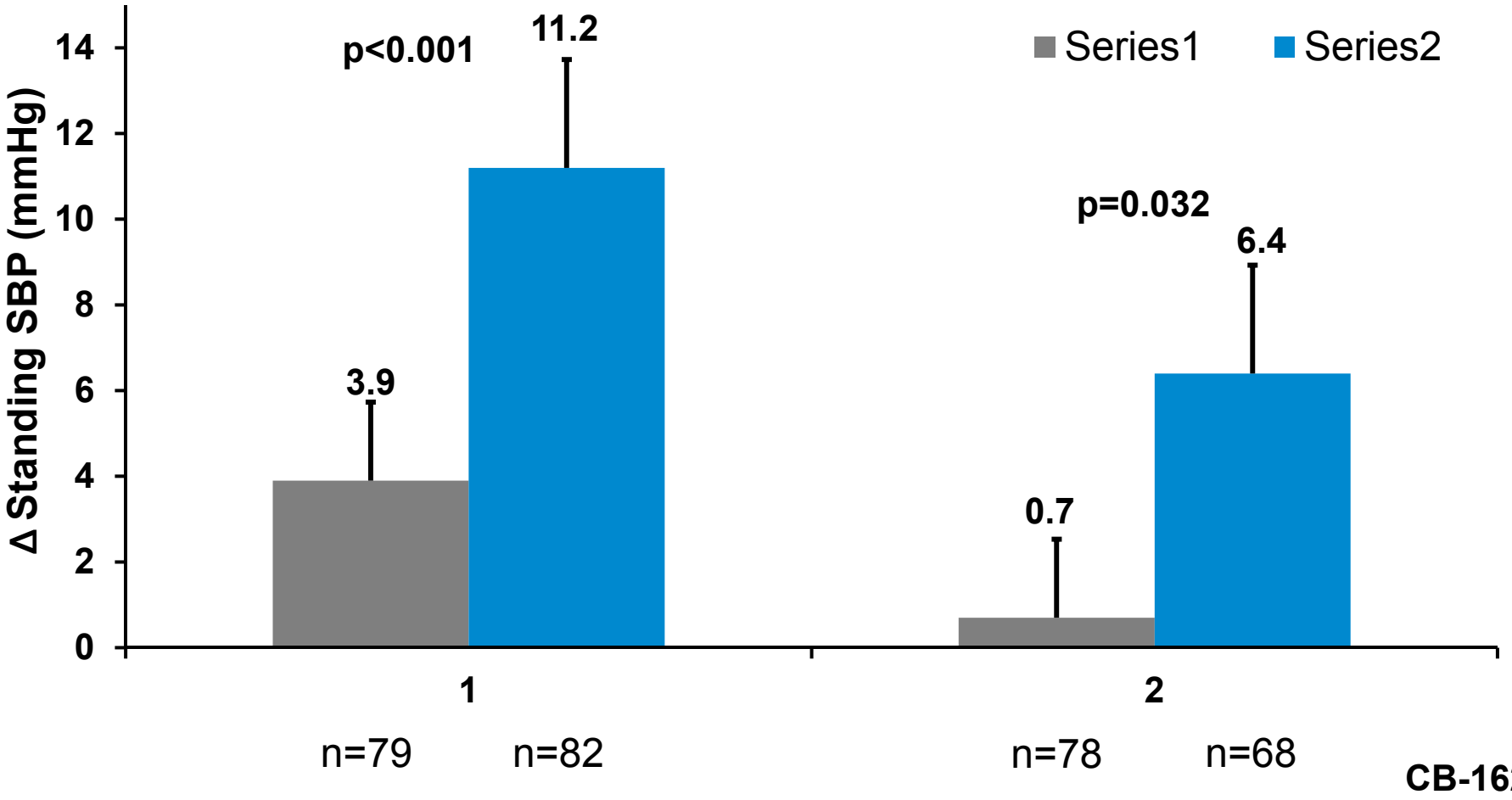
Evaluation of Benefit / Risk of Droxidopa Therapy

Limitations of Current Treatment Strategies for Neurogenic Orthostatic Hypotension (nOH)

- Clinicians have had to rely on non-pharmacologic therapies and drug therapies not approved for nOH
  - Increased salt intake
  - Waist high stockings
  - Fludrocortisone acetate, pyridostigmine
- Midodrine, a potent vasoconstrictor, is approved by FDA based on studies measuring standing BP
  - Midodrine's use is limited by supine hypertension and urinary retention
  - Not all patients respond

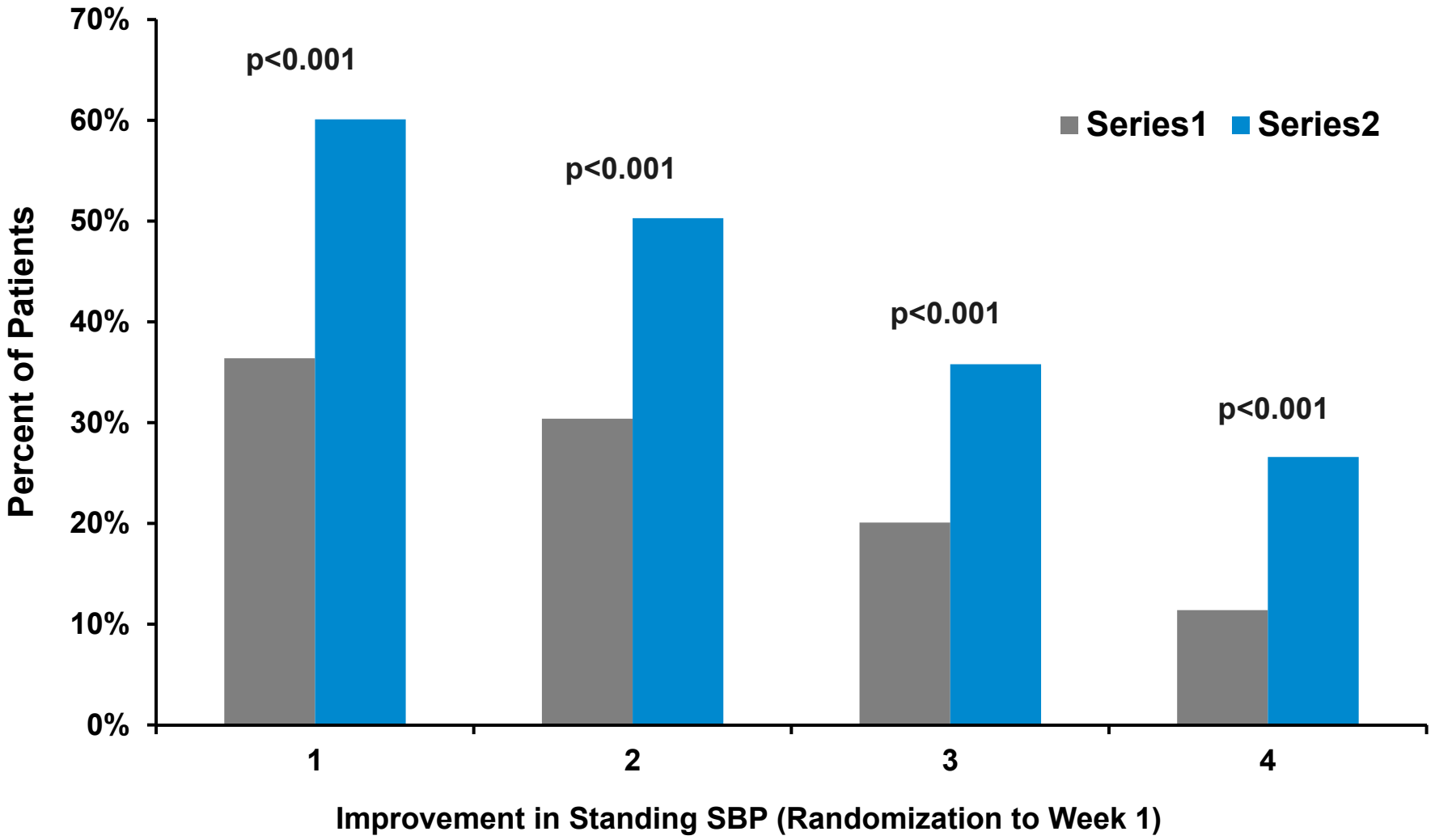
Droxidopa Improves Standing Blood Pressure in nOH Patients

Change in Standing SBP From Randomization to Week 1

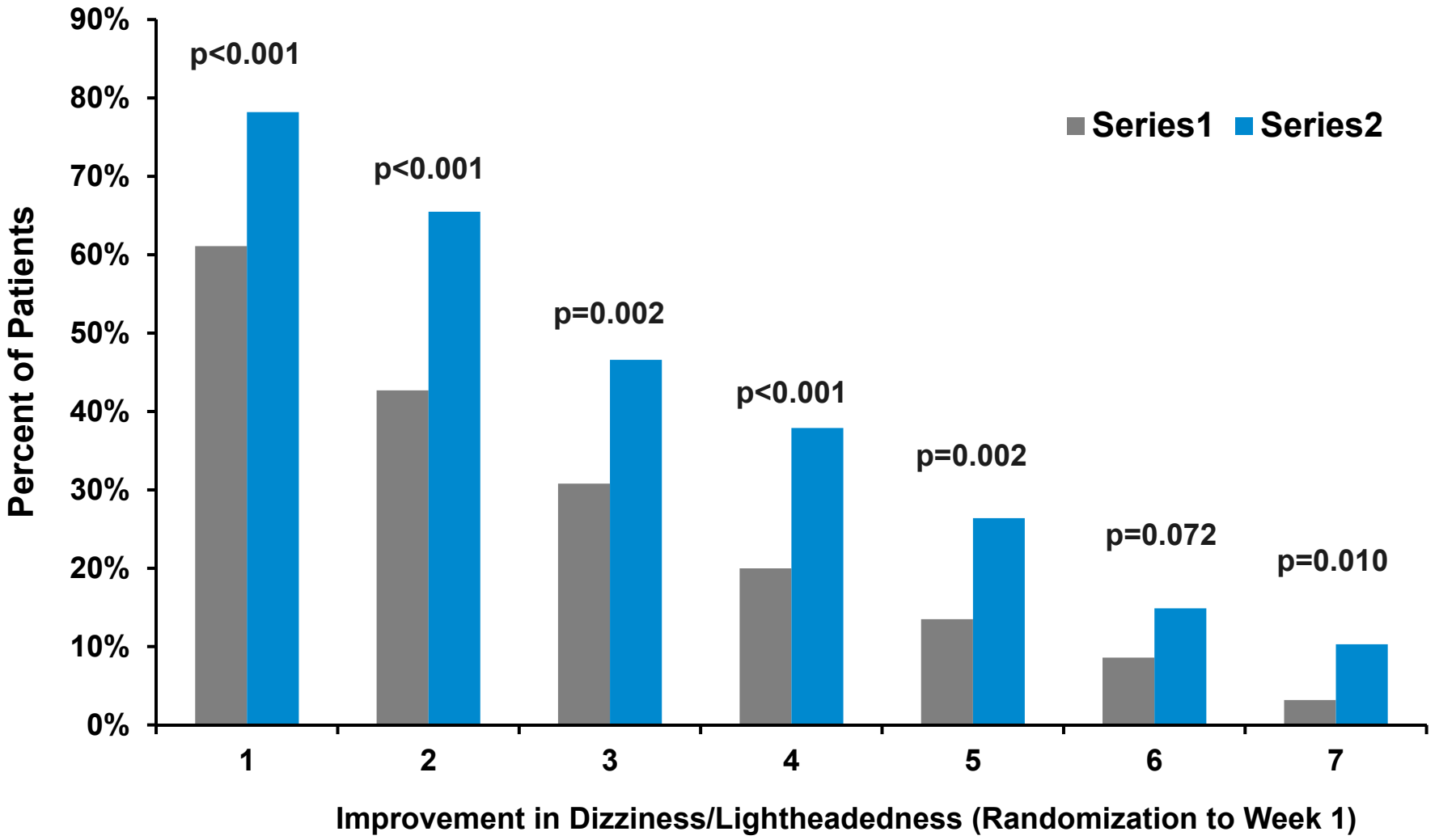


CB-162

Droxidopa has Clinically Meaningful Effects on Standing SBP (Study 301, 306)

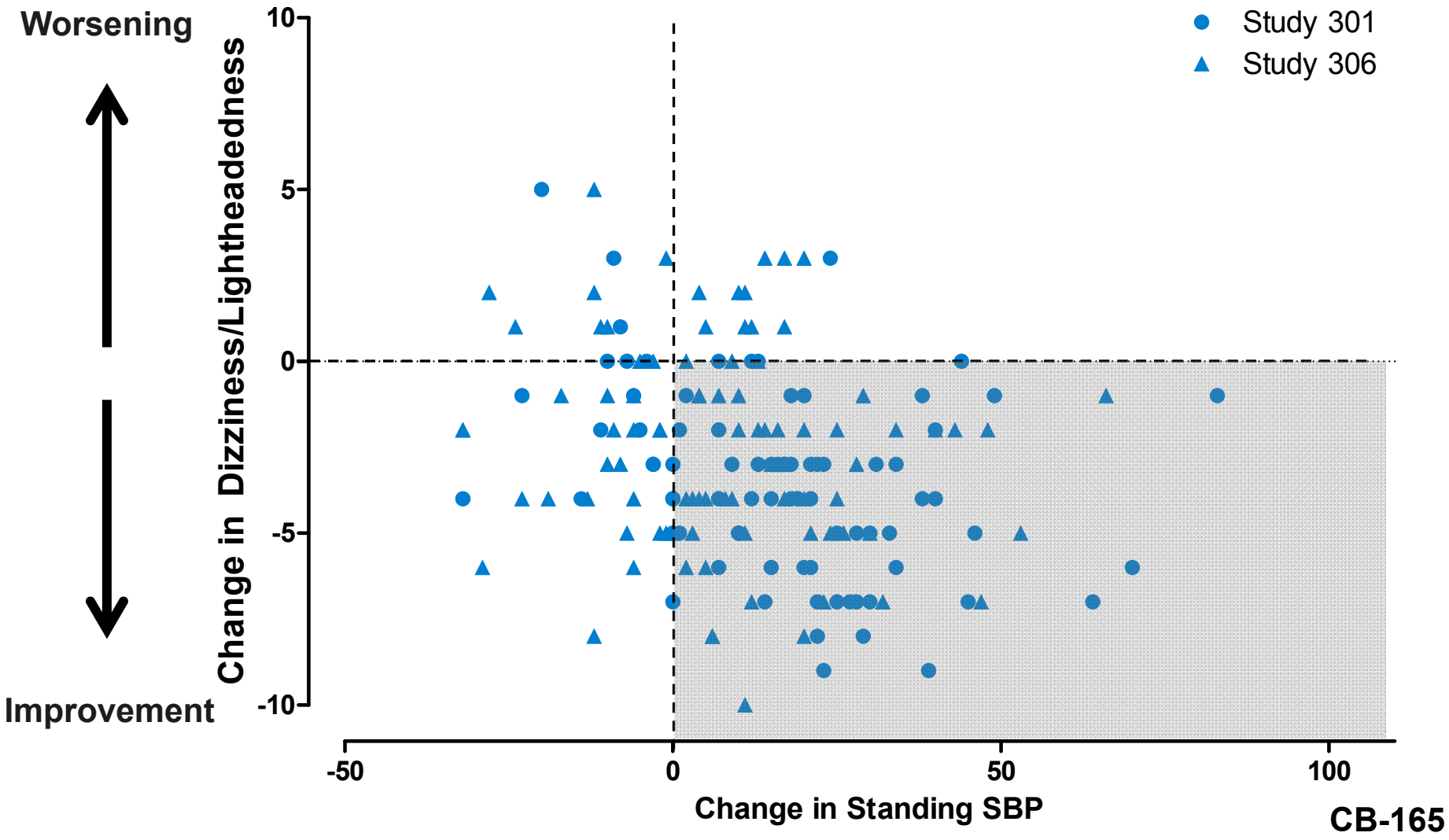


Droxidopa Improves Lightheadedness in nOH (Study 301, 306)



CB-164

Relationship in Symptoms & Standing SBP (Study 301, 306 Droxidopa Patients)

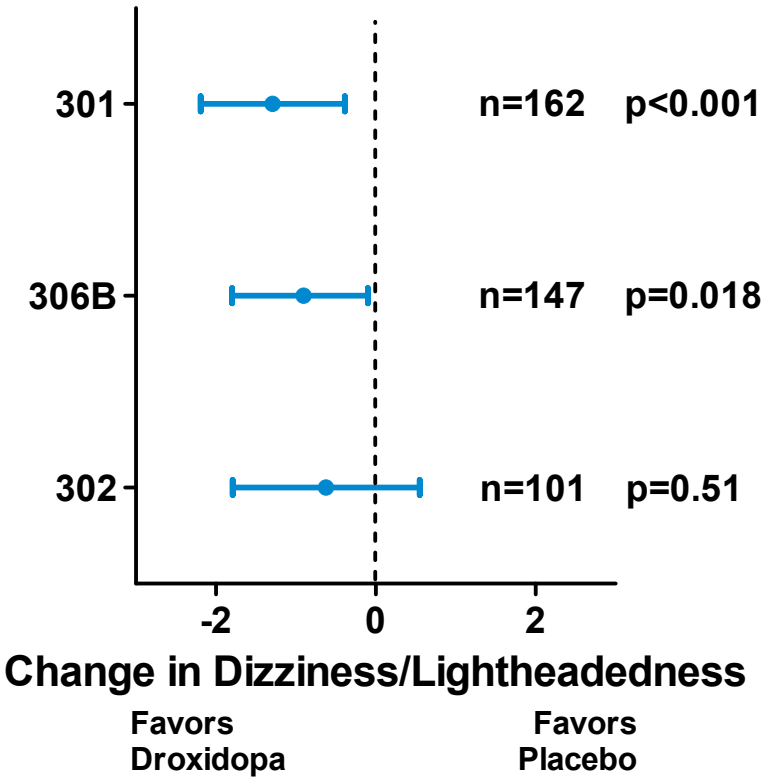


Study 306B: Fall-Related Injuries Were Lower on Droxidipa versus Placebo

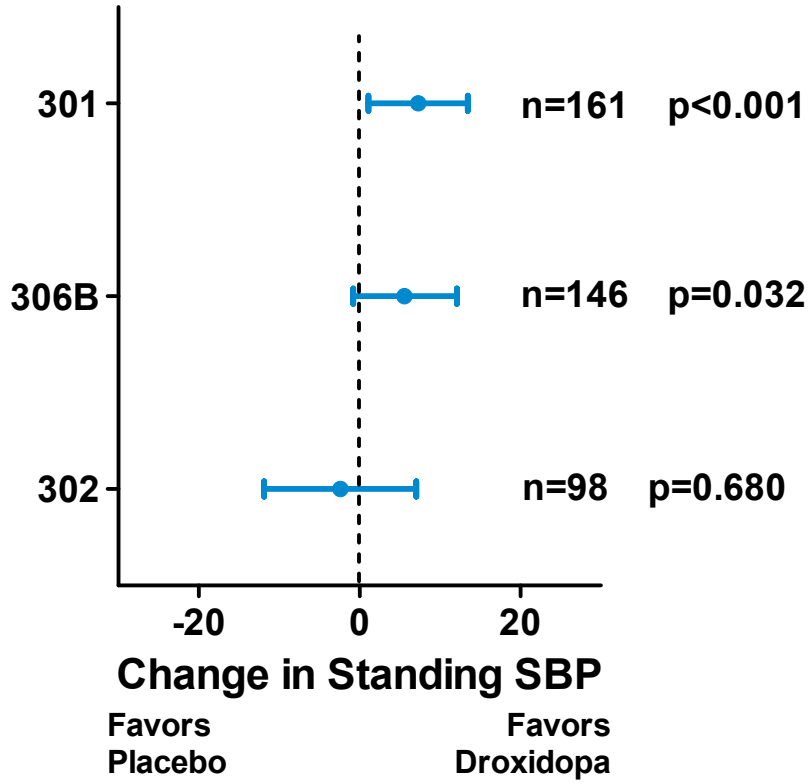
- A higher proportion of placebo patients (25.6%) experienced an injury related to a fall compared to droxidopa-treated patients (16.9%)
- Injuries included contusions (12.2% versus 3.4%), skin lacerations (8.5% versus 3.4%), and skin excoriations (8.5% versus 5.6%)
- One placebo patient experienced a fall related SAE of lower extremity fracture

Consistency for Short-term Improvements in Symptoms and Standing BP in nOH Patients

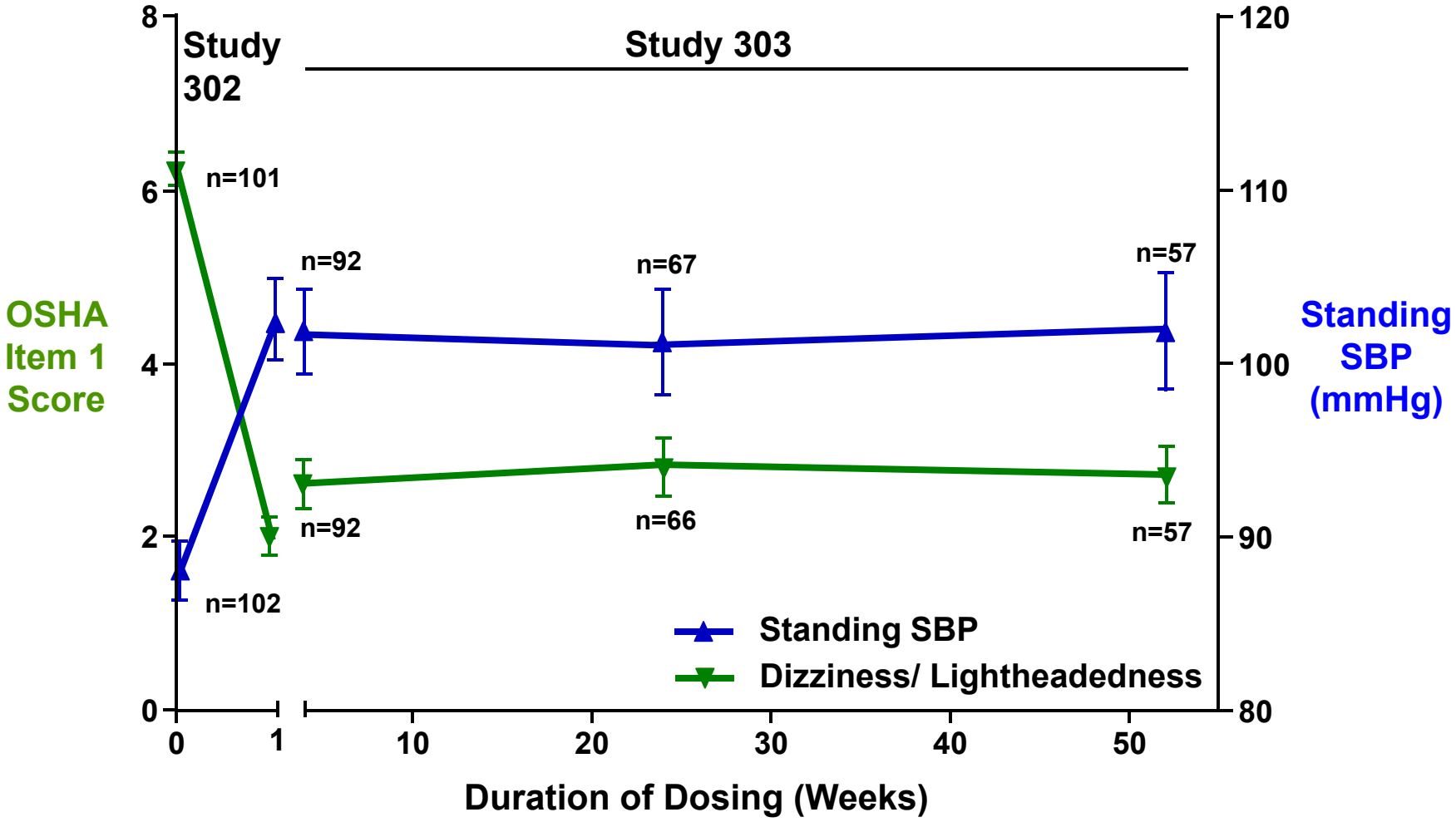
Symptoms



Blood Pressure

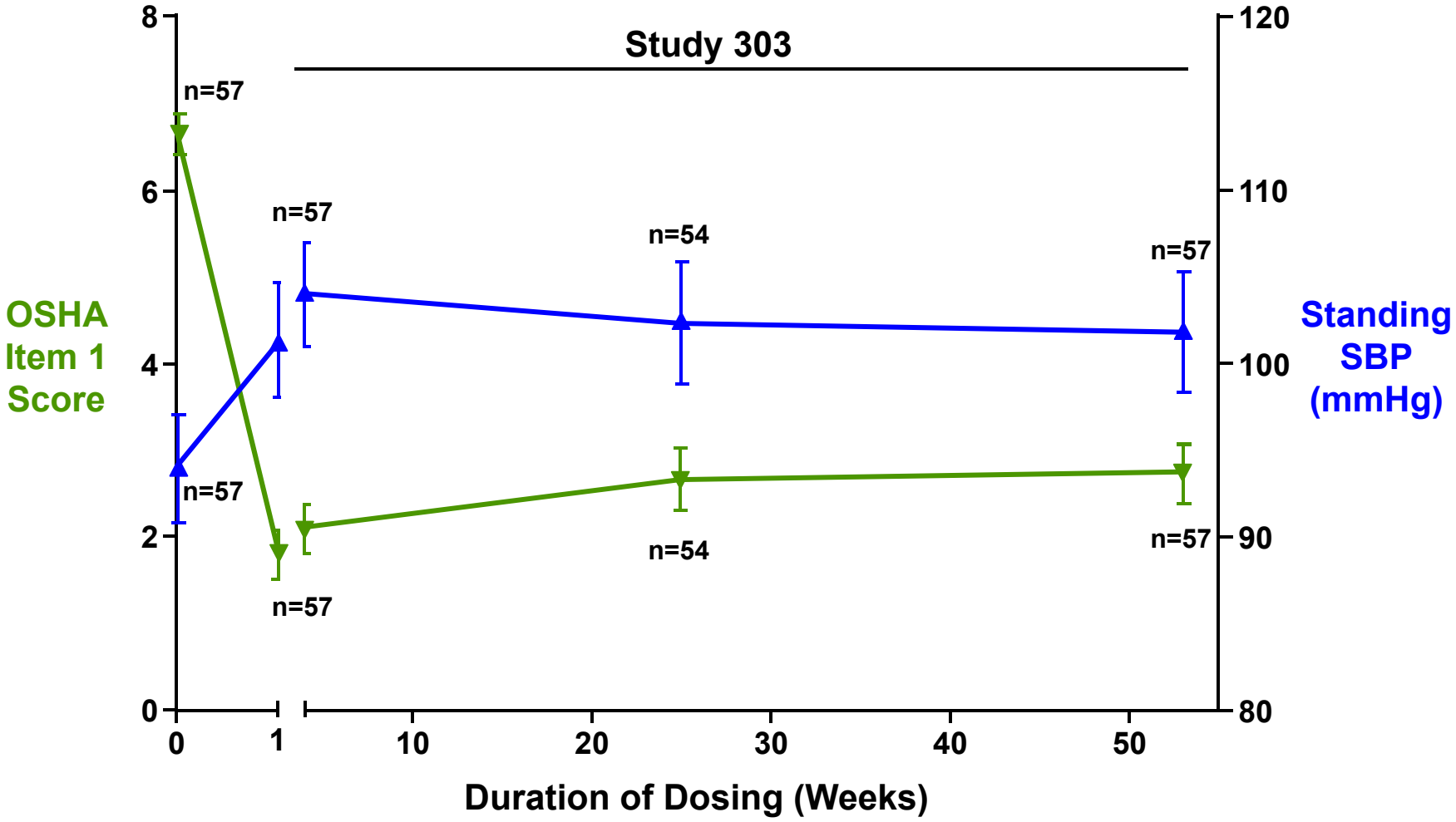


Study 303:
Long-Term Open-Label Extension



CB-168

Durability Trends in Study 303 for Standing Systolic BP + OHSA Item 1



CB-169

Limitations of Droxidopa Database

- Primarily short-term benefits have been shown
  - Some evidence of sustained benefit seen in the extension study
- Interpretation of adverse events in an uncontrolled extension studies is difficult
  - Death rates, serious events and severe hypertension are similar to those observed in cohorts who have been followed longitudinally with nOH

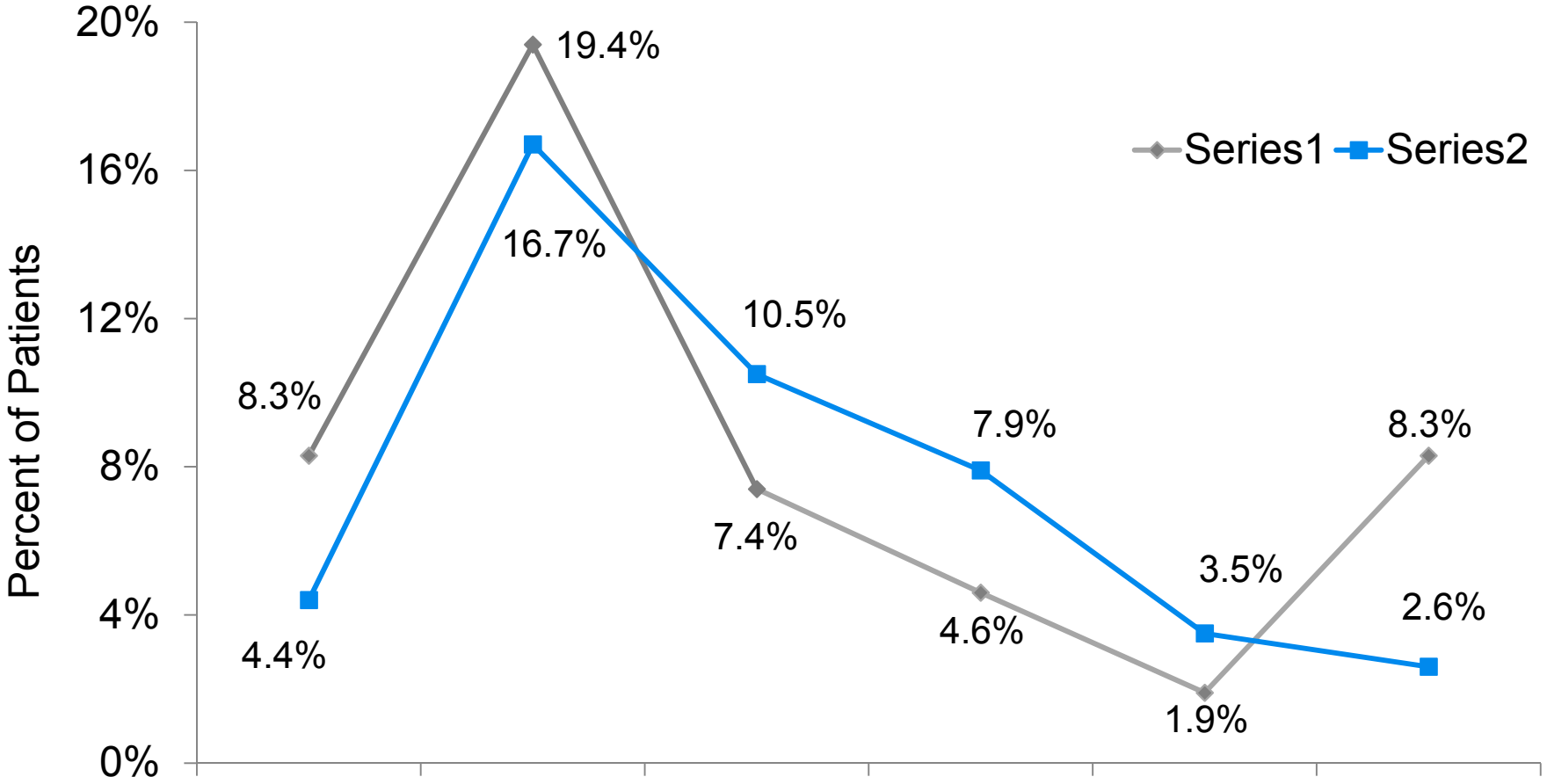
Benefit Risk Conclusion for Droxidopa in Patients with nOH

Droxidopa at doses of 100-600 mg three times daily in nOH patients:

- Provides an effective therapy in an important minority of this orphan subpopulation of neurodegenerative diseases
- Has an acceptable safety profile (supine hypertension is a risk but manageable), particularly considering the debilitating nature of this disorder
- Results in clinical improvements that translate into meaningful benefits to the patient with nOH

Sponsor Backup Slides Shown

Supine SBP >160mmHg
Randomized Patients: Overall Study 306

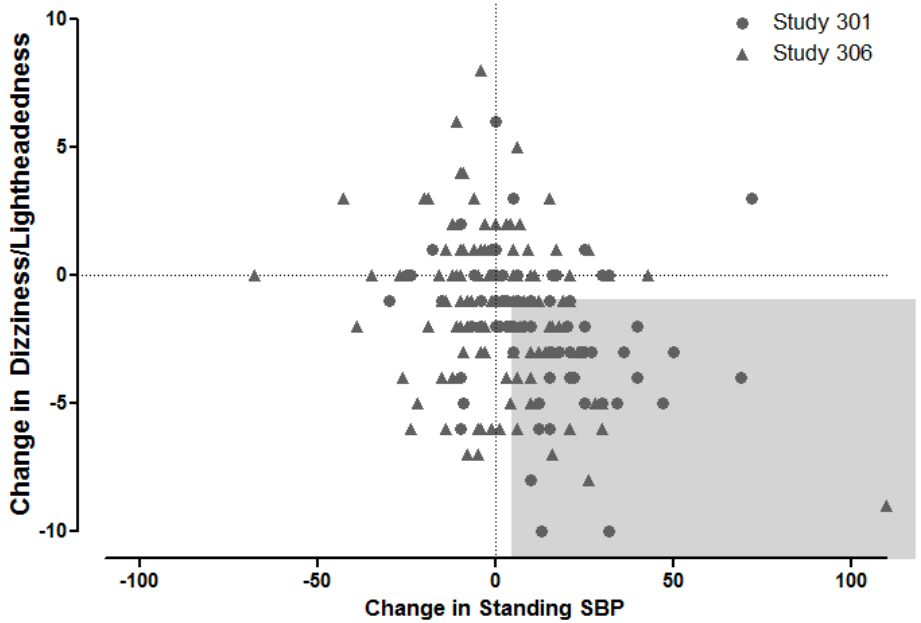


Placebo N=	108	108	106	101	96	93
Droxidopa N=	114	112	107	94	90	86

CV-66

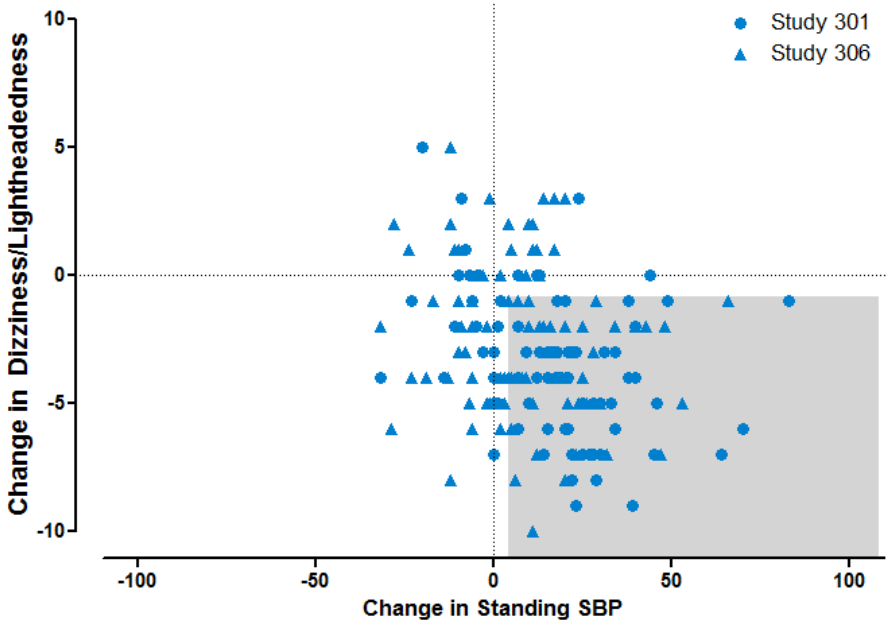
Relationship in Symptoms, Standing SBP (Study 301, 306)

Placebo Patients



35.3% of Placebo Patients had both 5mmHg and 1 unit improvement

Droxidopa Patients



56.3% of Droxidopa Patients had both 5mmHg and 1 unit improvement

p<0.0001

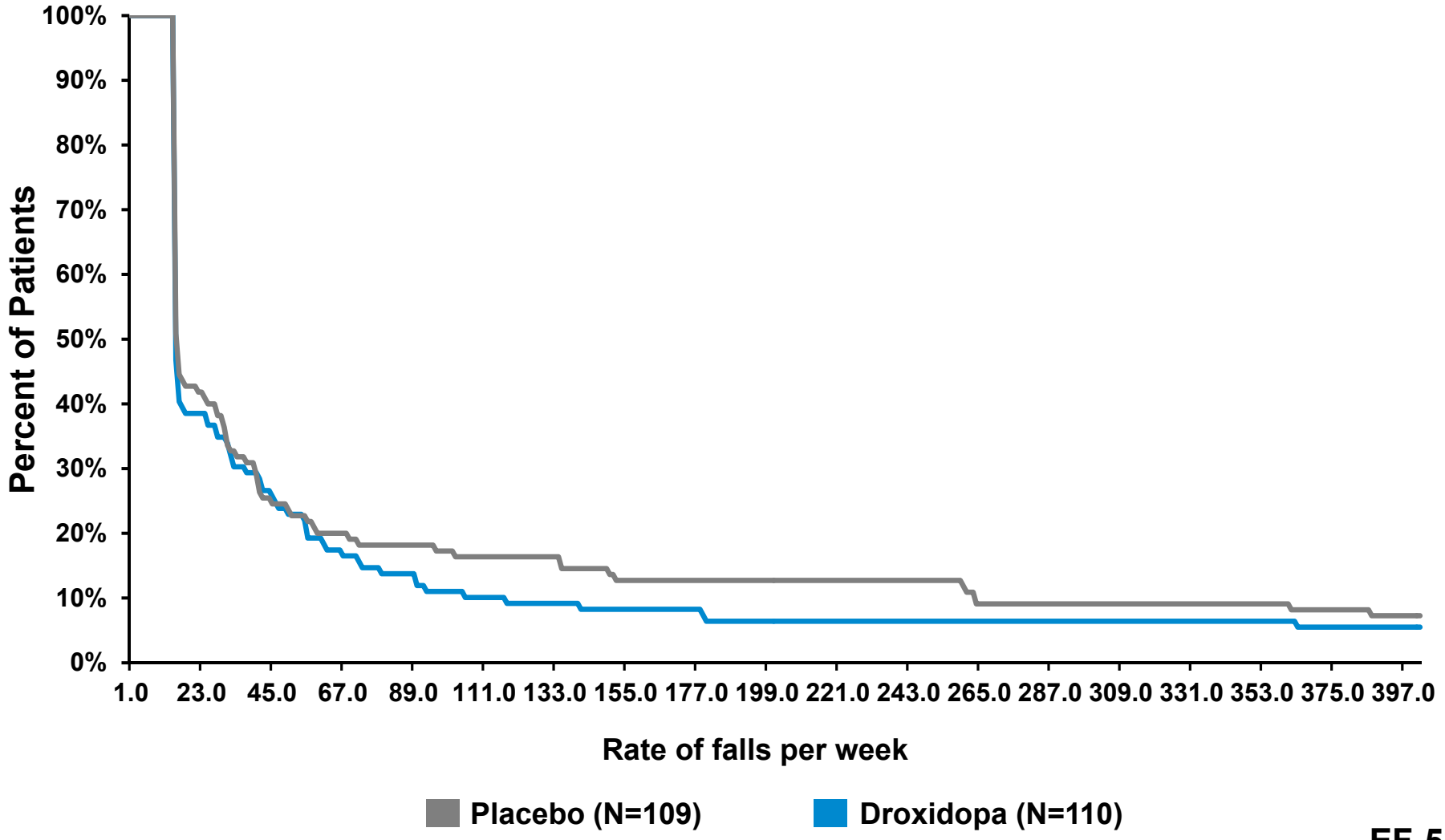
EF-578

Numerous Evaluations Show No Evidence of Tachyphylaxis

- DBH patients: chronic use (decades) show no loss of effect
- No down-regulation of platelet α2-adrenergic receptors with chronic droxidopa treatment[1]
- No change in pressor response to infused NE and isoproterenol after 5 weeks of droxidopa in FAP patient[2]
- Pressor response to droxidopa unchanged after 31 months of treatment in acute pandysautonomia patient[3]

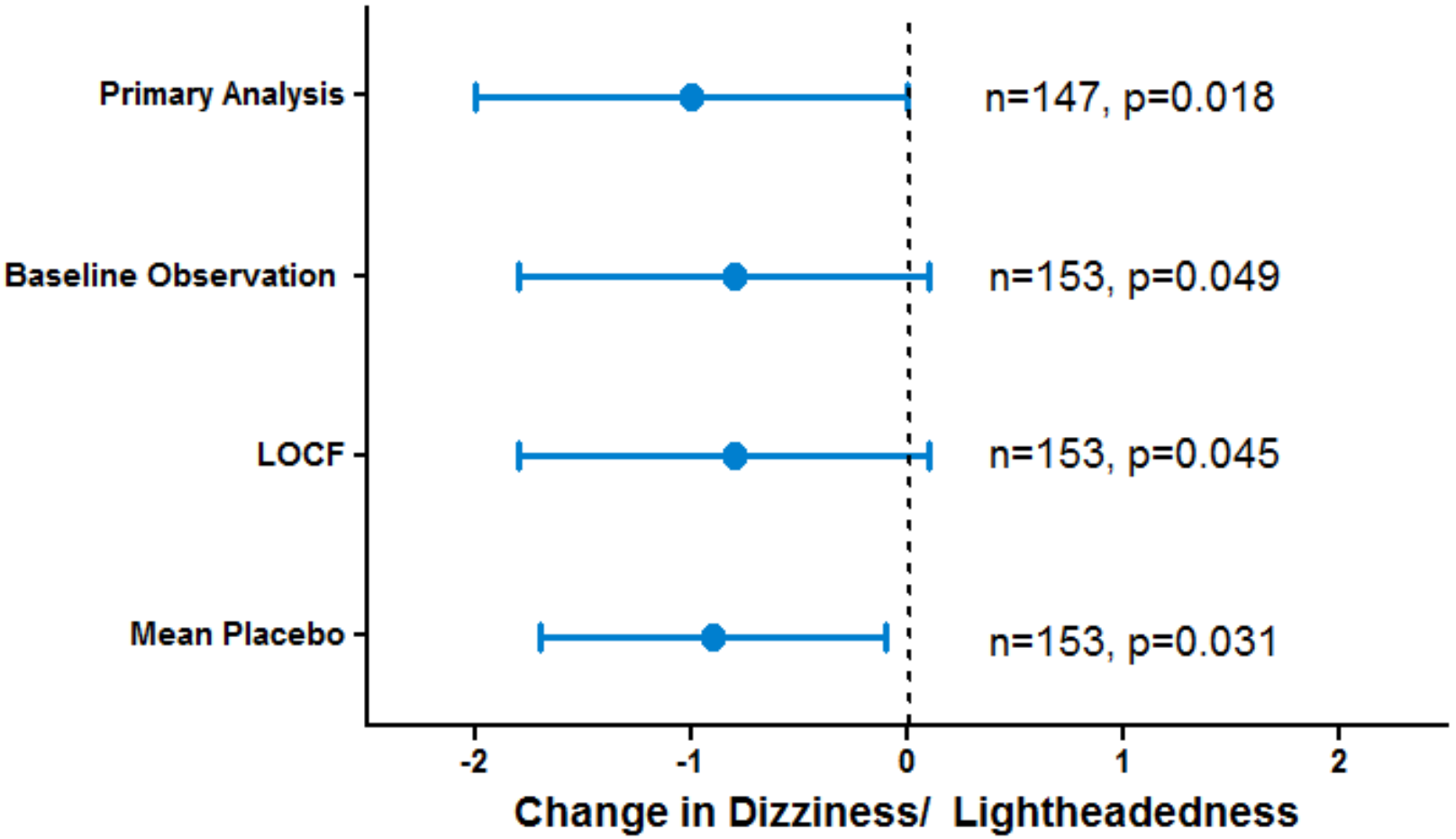
[1] Azuma et al, 1991; [2] Azuma et al, 1988; [3] Ushiyama et al, 1996

Study 306B + Interim Analysis Dataset:
Rate of Falls Per Week (ITT)



EF-584

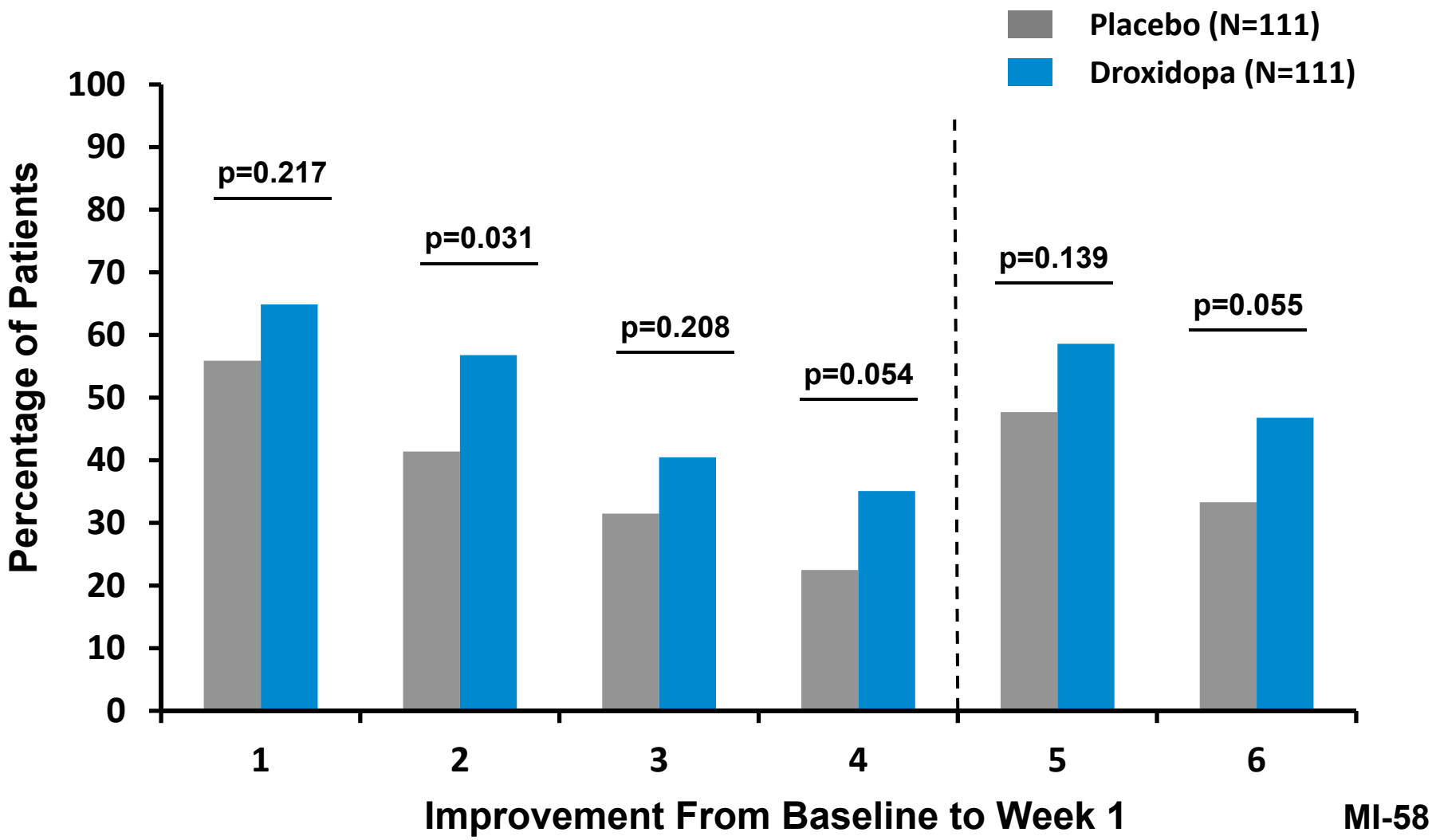
Study 306B: Change in Dizziness
Patients Completing Titration



Study 306B:
Patient Demographics (FAS)

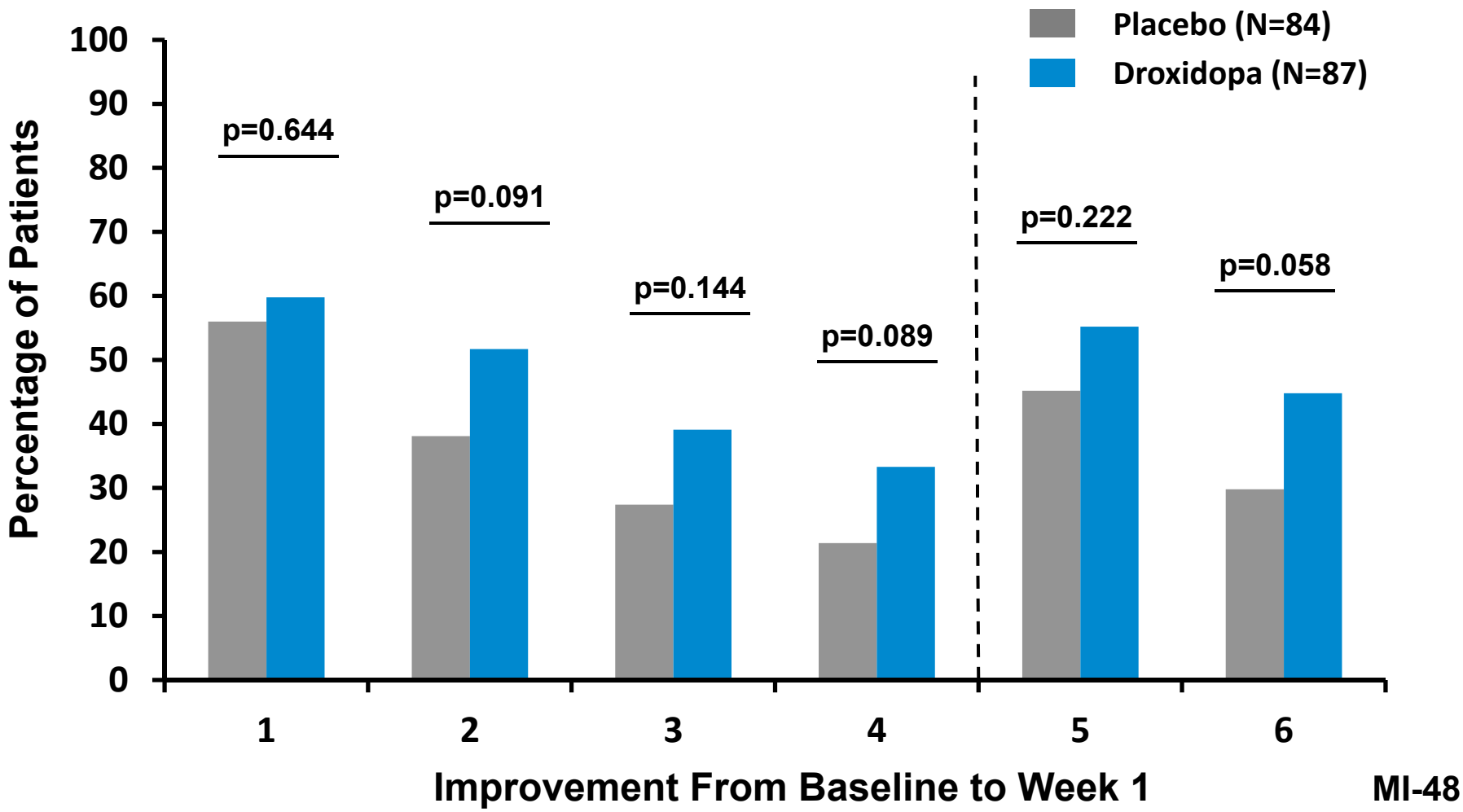
		Randomized-Controlled Phase	
		Placebo (N=78)	Droxidopa (N=69)
Primary Diagnosis: n (%)	PD	78 (100.0)	69 (100.0)
Sex: n (%)	Male	52 (66.7)	45 (65.2)
	Female	26 (33.3)	24 (34.8)
Race: n (%)	White	75 (96.2)	65 (94.2)
	Other	3 (3.8)	4 (5.8)
Age at Screening:	Mean [range]	71.9 [54,86]	72.5 [41,92]
Geographic Region: n (%)	US	78 (100.0)	69 (100.0)
Baseline Disease Severity			
	Dizziness/Lightheadedness, units (SD)	5.1 (2.33)	5.1 (2.04)
	Mean Lowest Standing SBP, mmHg (SD)	95.7 (20.09)	94.7 (21.53)

Study 306B + Interim Dataset, Week 1: Dizziness/Lightheadedness Response (ITT)



MI-58

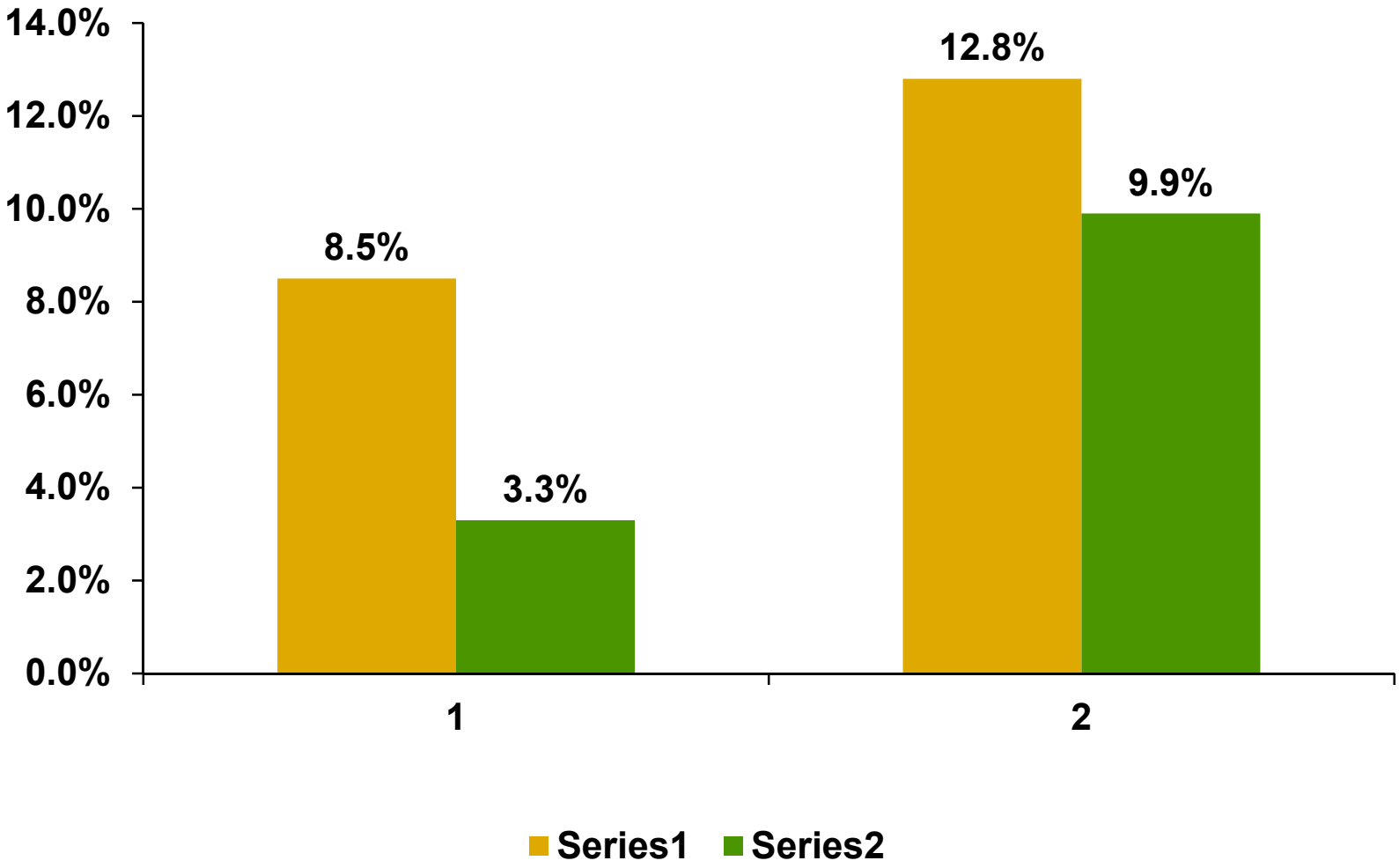
Study 306B (ITT, N=171): Dizziness Responders at Week 1



MI-48

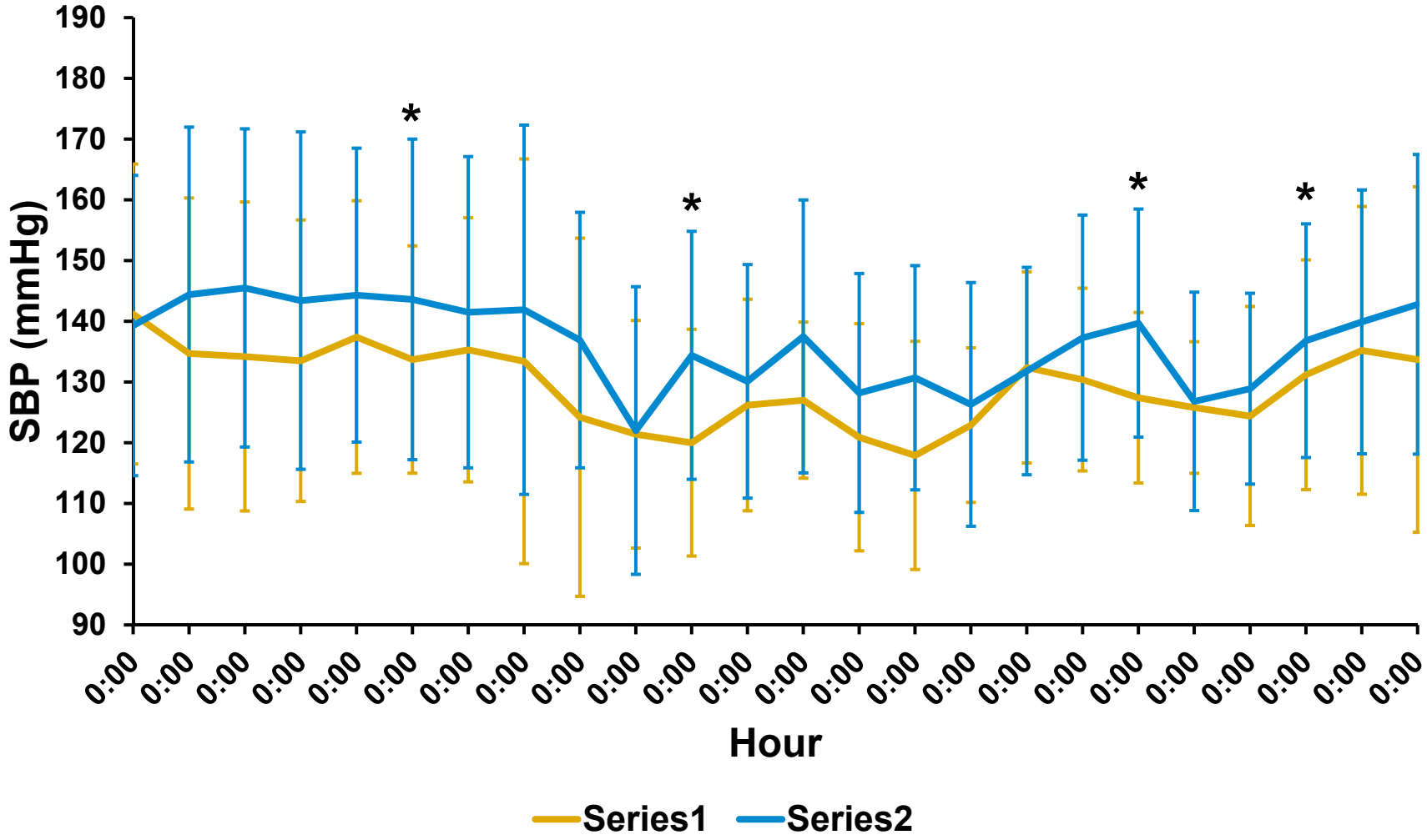
Supine Hypertension, Patients Previously On Midodrine Only; Midodrine vs. Droxidopa

Studies 301 and 302



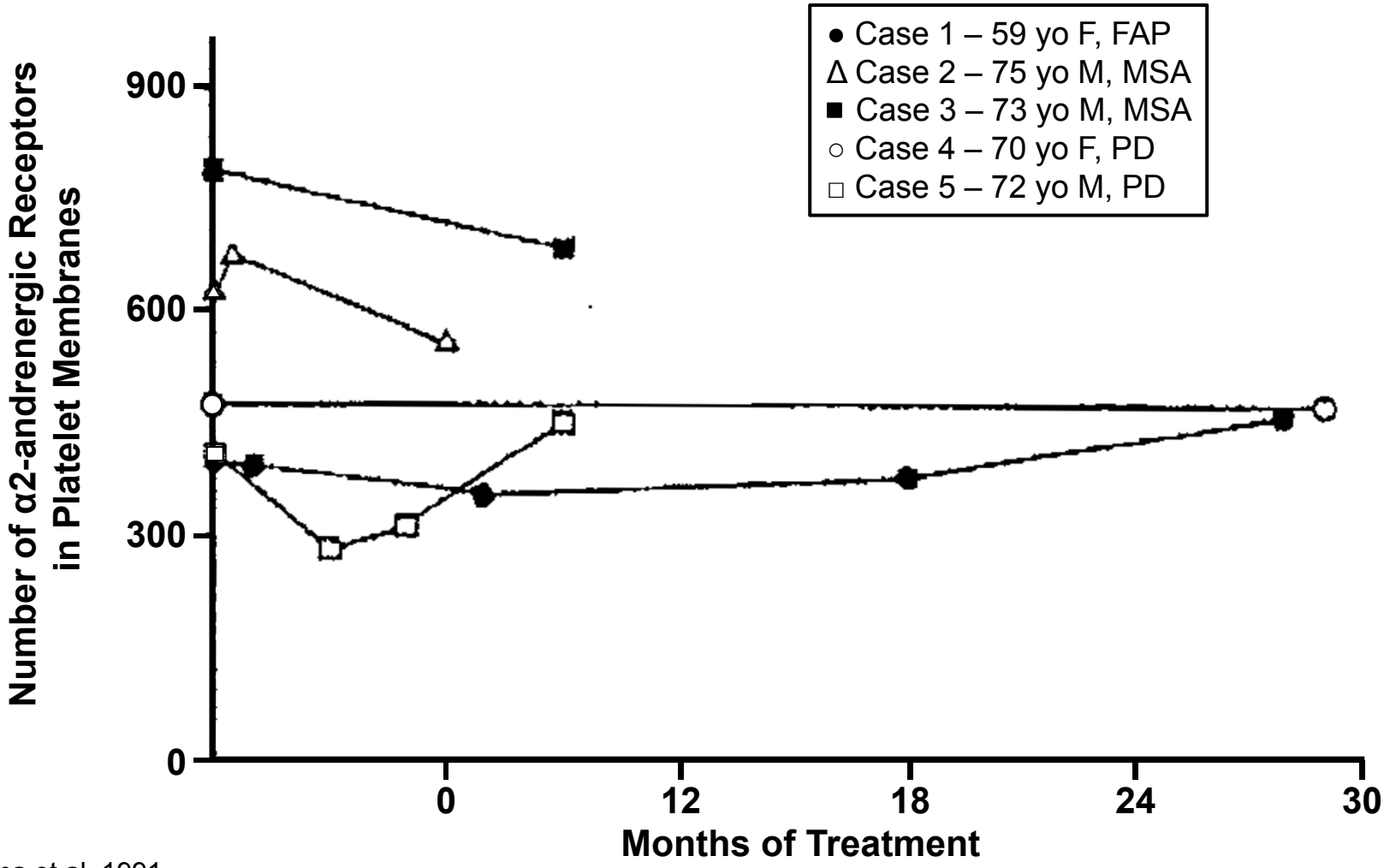
CV-056

Study 305: 24-Hour SBP Profile



*p≤0.05

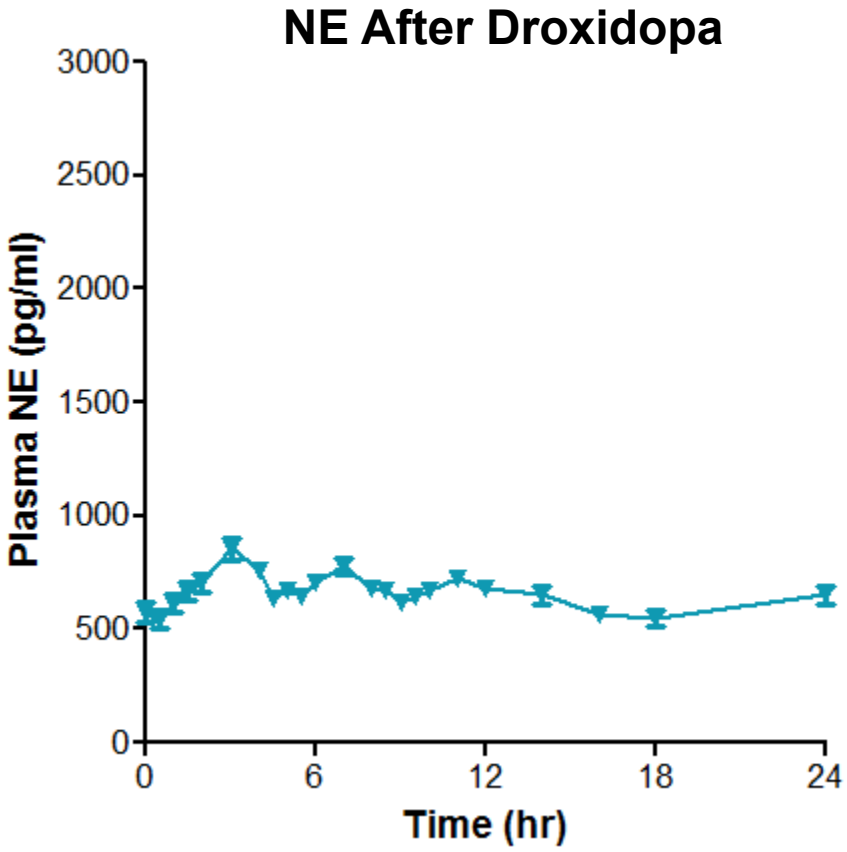
The Changes of the Number of α2-andrenergic Receptors Isolated from Patients During Therapy with Droxidopa



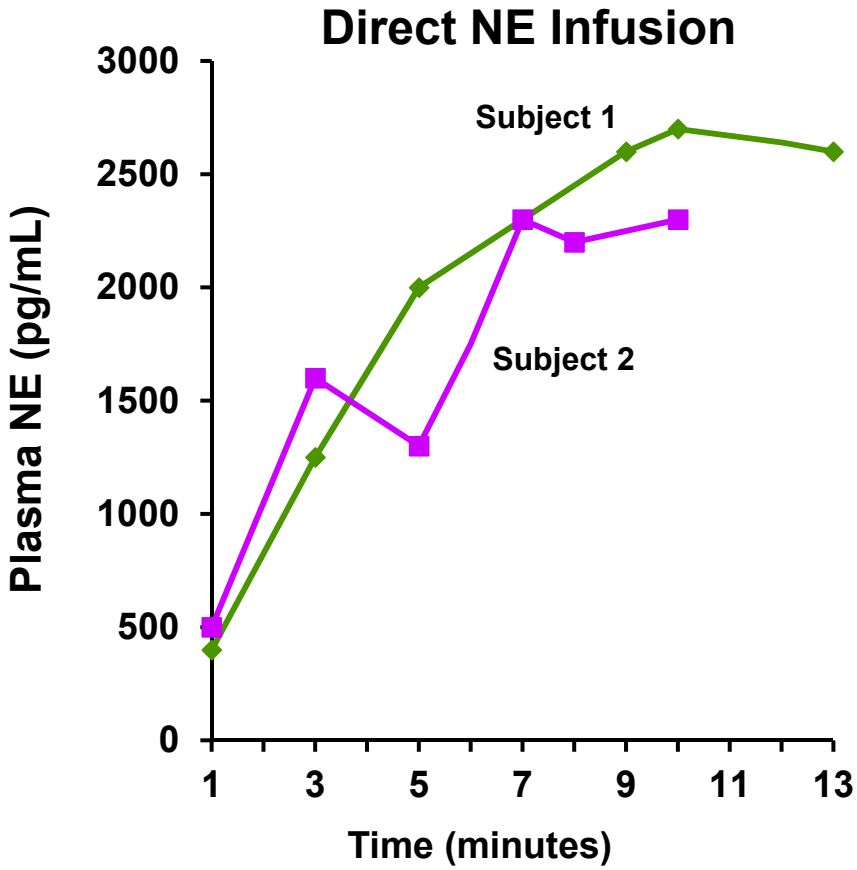
Azuma et al. 1991.

BG-154

Plasma NE Concentration: Droxidopa vs NE Infusion



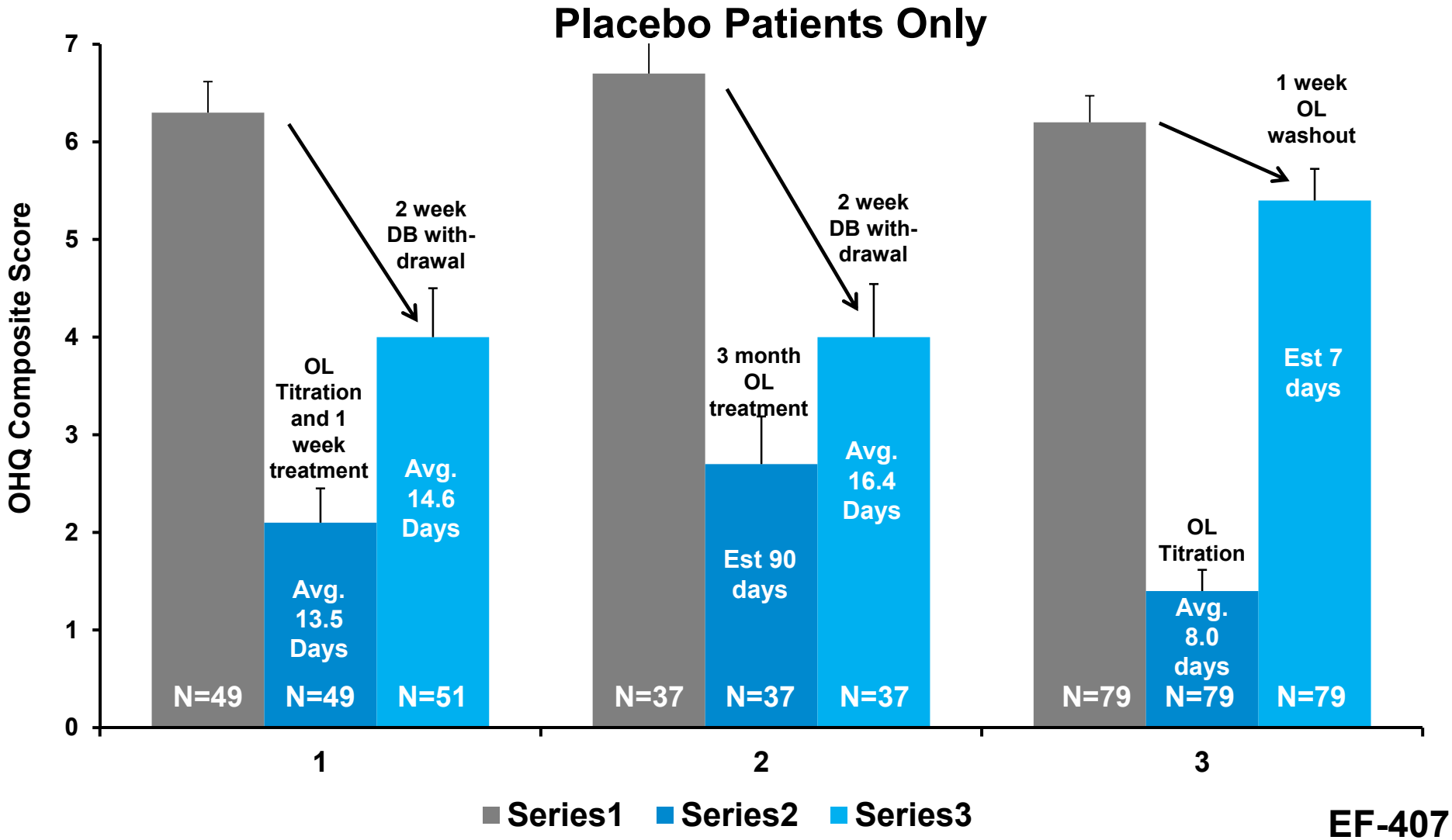
Chelsea Study 101; N=24



Adapted from "Plasma Concentrations of Epinephrine and Norepinephrine during Intravenous Infusions in Man", *J Clin Invest*. 1959; 38(11):1935–1941.

PK-001

After Withdrawal of Droxidopa Symptoms Do Not Return to Baseline



EF-407

OHQ Scale: Concept Validation Study (n=20)

OHQ Item	% Patients with Symptom
Dizziness/Lightheadedness presyncope	95%
Problems with vision	25%
Weakness	45%
Fatigue	50%
Trouble Concentrating	25%
Head/Neck Pain	10%
Standing Short Time	40%
Standing Long Time	50%
Walking Short Time	35%
Walking Long Time	45%

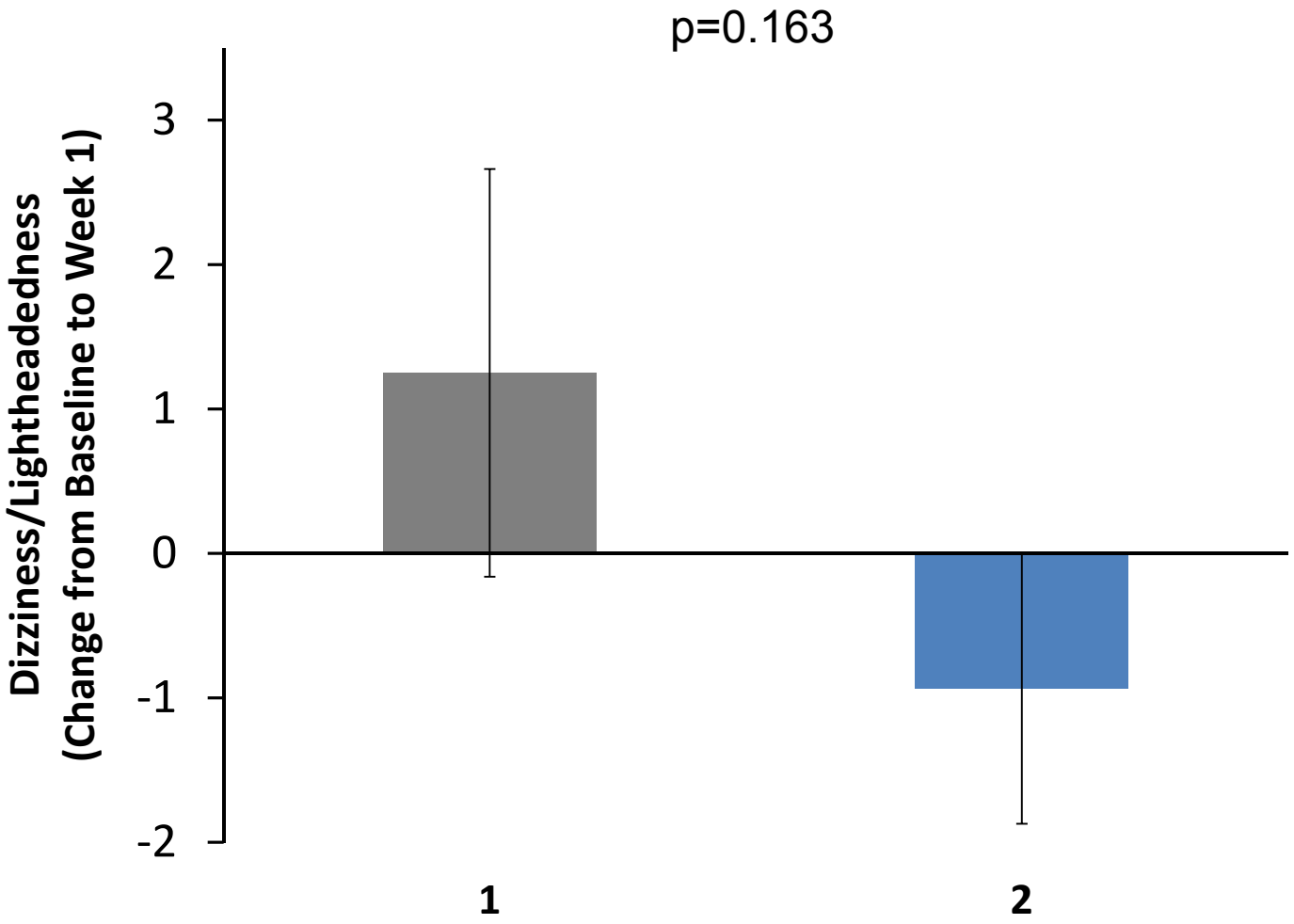
- Patients interviewed about symptoms and how they impact their daily activities
- Asked "*What symptoms do you experience related to your orthostatic hypotension/low blood pressure?*"
- Responses categorized to match items within the OHQ
- Dizziness/ lightheadedness and presyncope was clearly the most common and universal symptom of NOH

BG-165

Minimally Important Difference Estimates: OHQ Composite Score

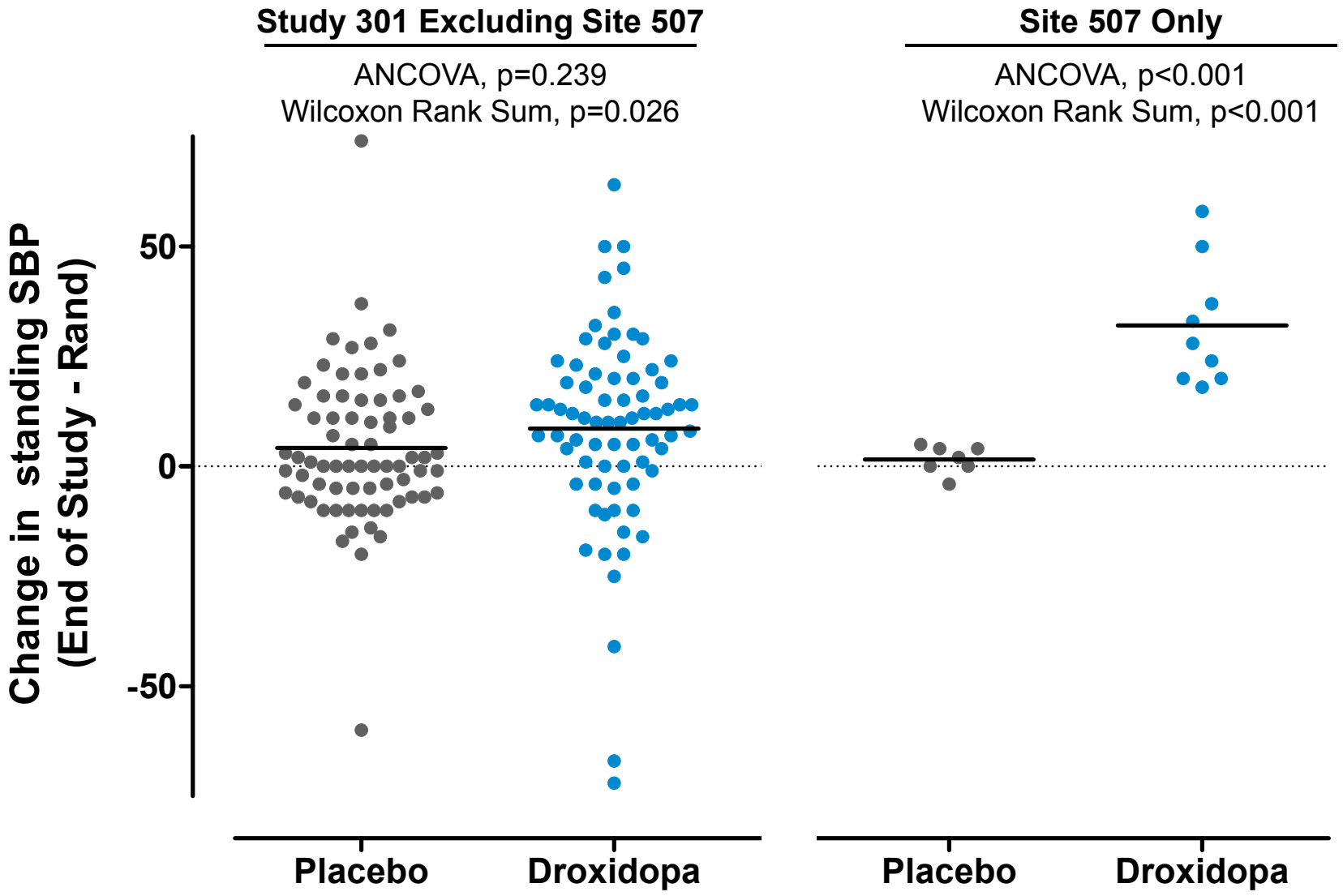
	Study 301		Study 306AB	
MID Analysis Method	**N**	**Units**	**N**	**Units**
Anchor Based				
Patient Global Improvement (slightly improved)	49	-1.99	53	-1.76
MDS-UPDRS Item 1.12 (1 unit improvement)	-	-	60	-2.24
Distribution Based				
½ Standard Deviation	263	1.12	225	0.79
Standard Error Measurement	22	0.52	38	1.02

Change Symptomatic Dizziness In Patients with AE of Dizziness (Study 306AB)



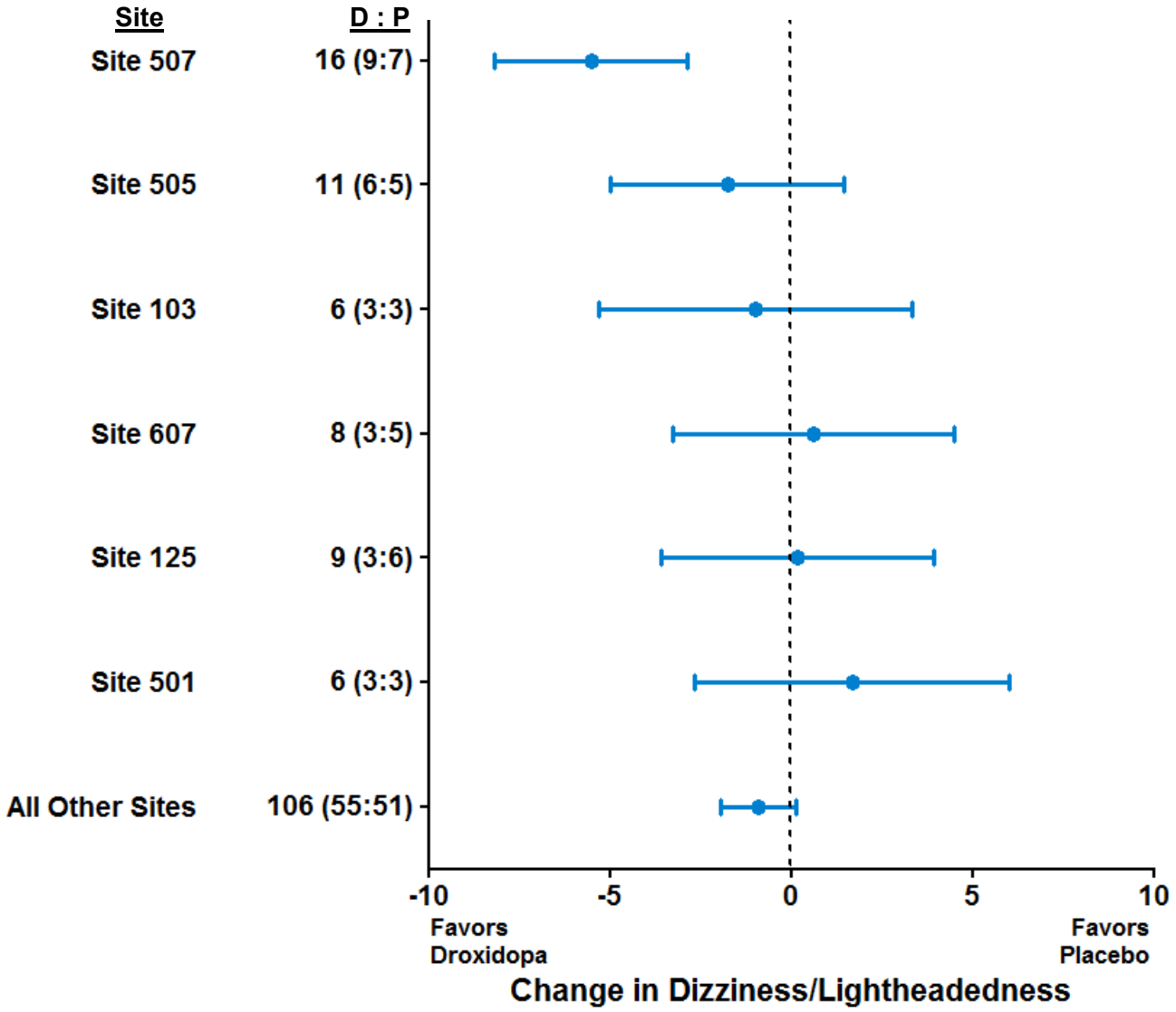
SA-453

Study 301 Site 507:
Mean Change Blood Pressure

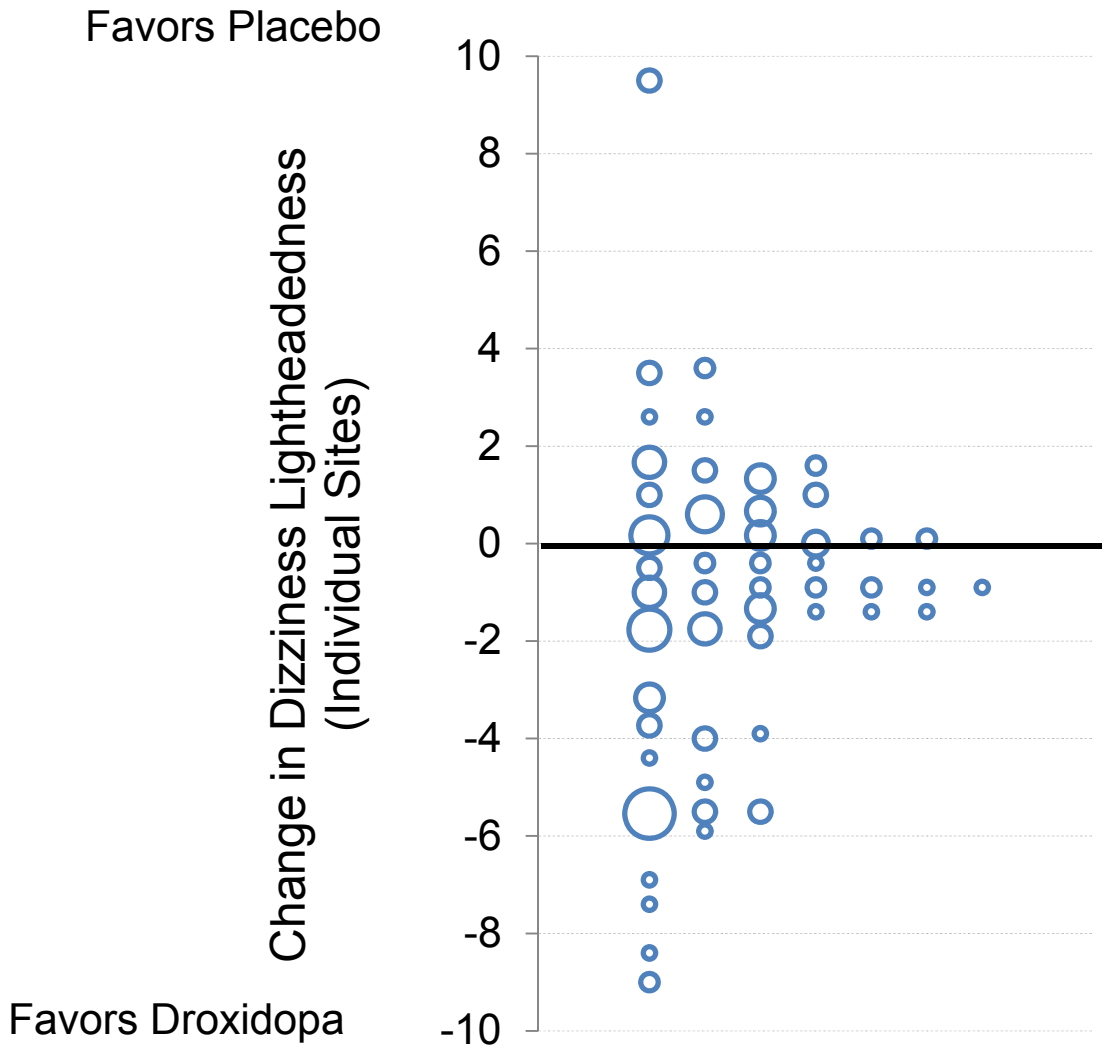


Study 301 Site Effects

Change in Dizziness/Lightheadedness



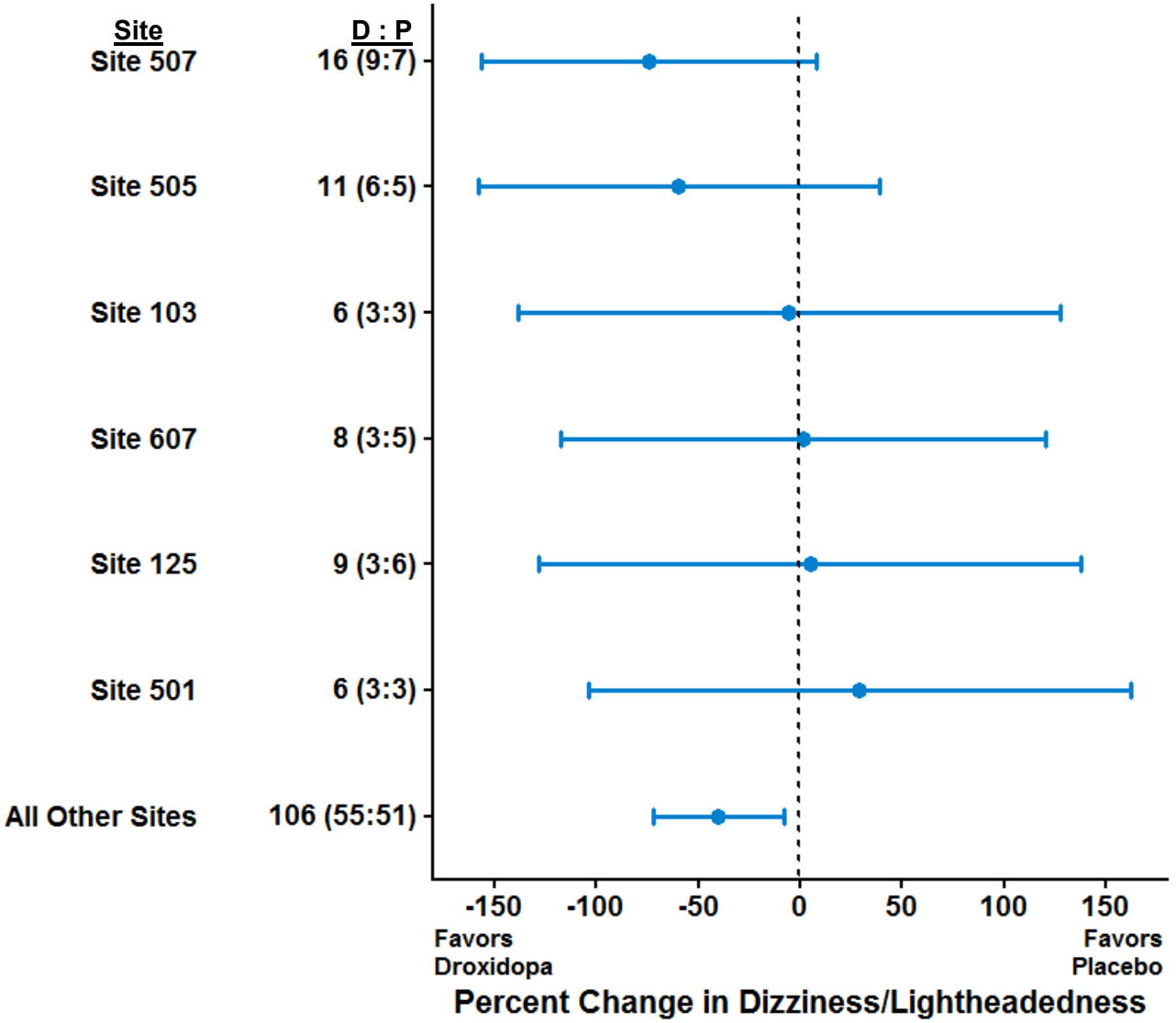
Treatment Effect Per Site
Study 301



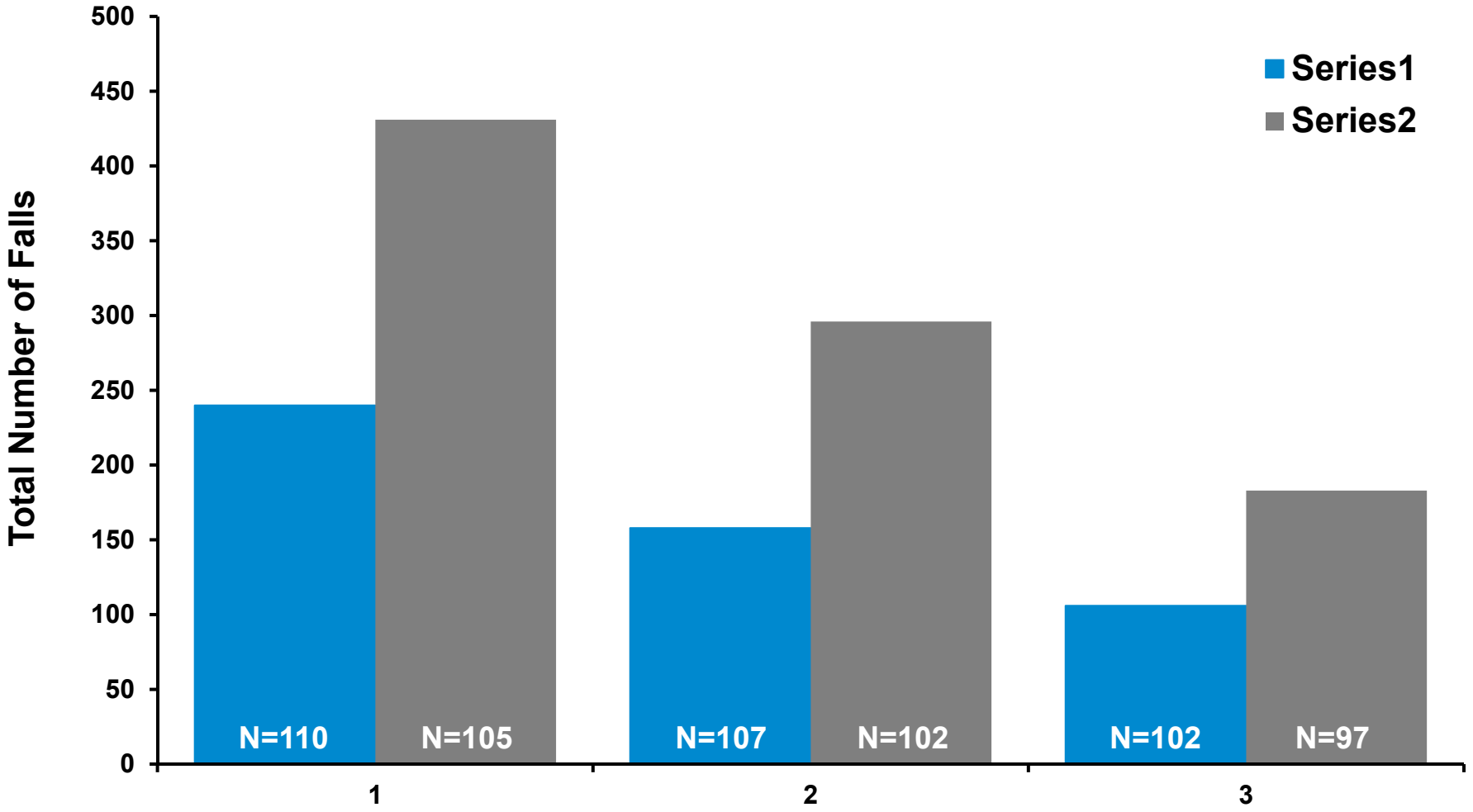
- Treatment Delta per site in Study 301
- Group Means imputed for sites without a patient in a treatment arm
- Site N = Bubble Size

Study 301 Site Effects

Percent Change in Dizziness/Lightheadedness

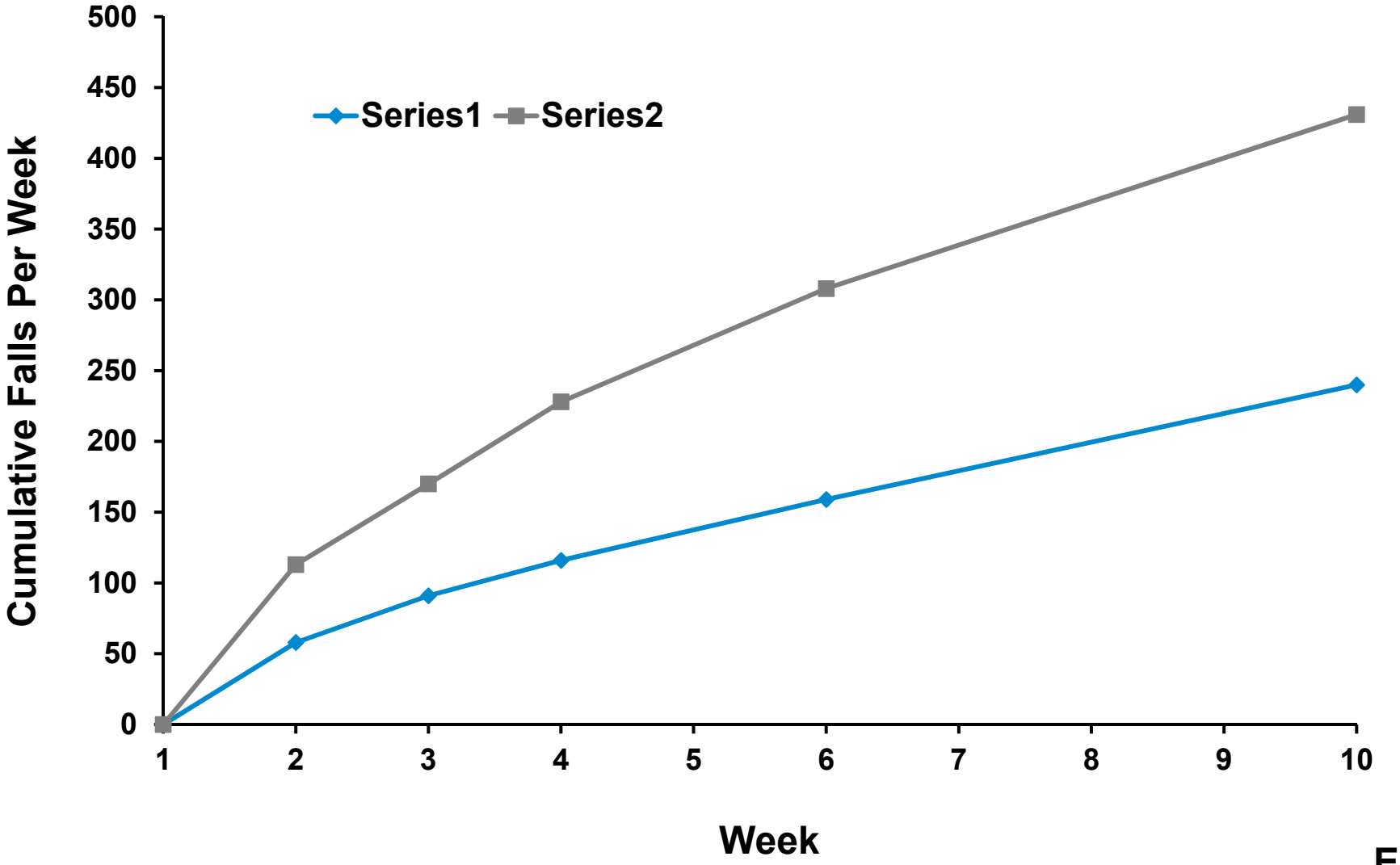


Study 306 Total Number of Falls:
Top 2, 5, 10 Fallers Removed



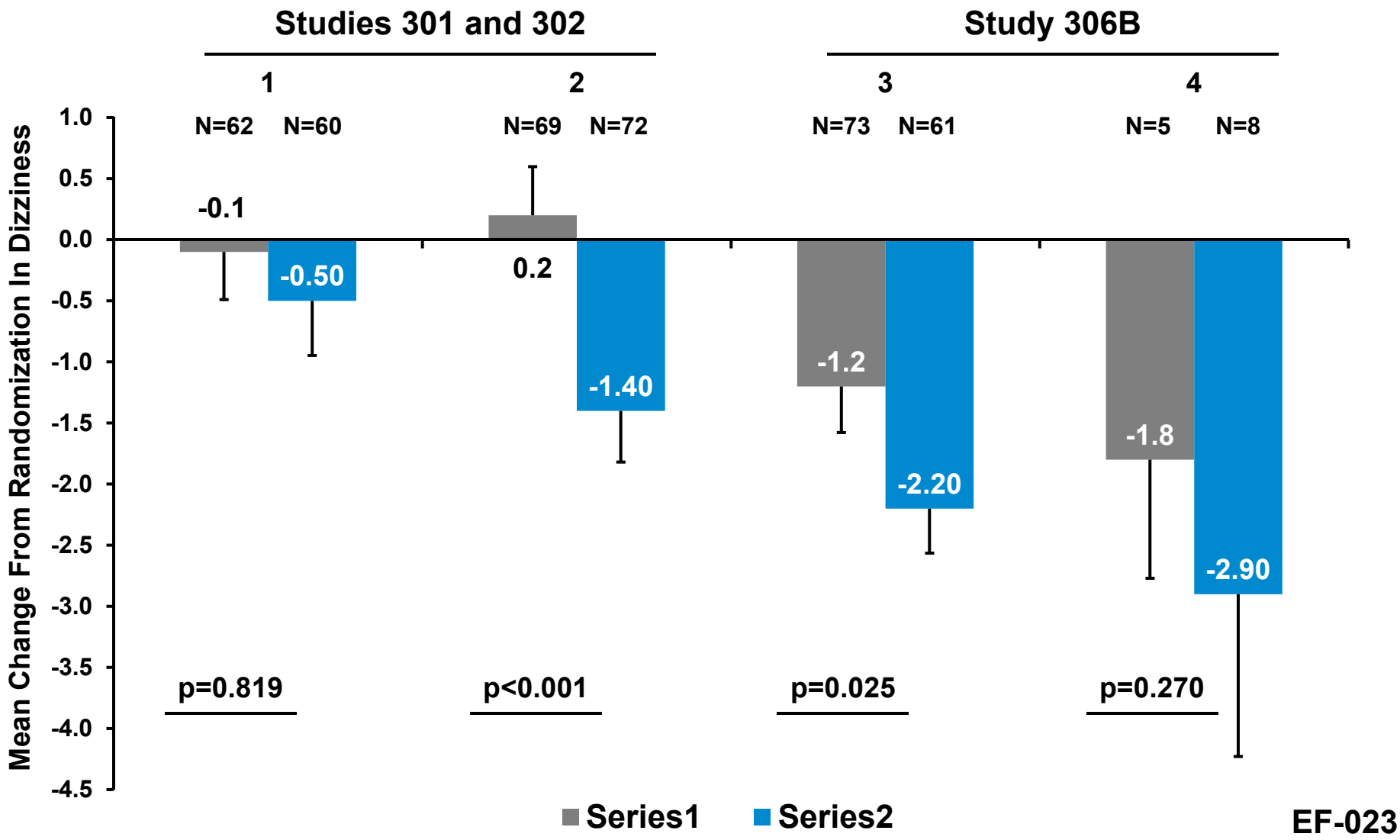
EF-399

Study 306AB Cumulative Falls Per Week: Top 2 Fallers Removed



EF-396

Studies 301 and 302; Study 306B:
Dizziness CFR - DDC-I Use:



EF-023

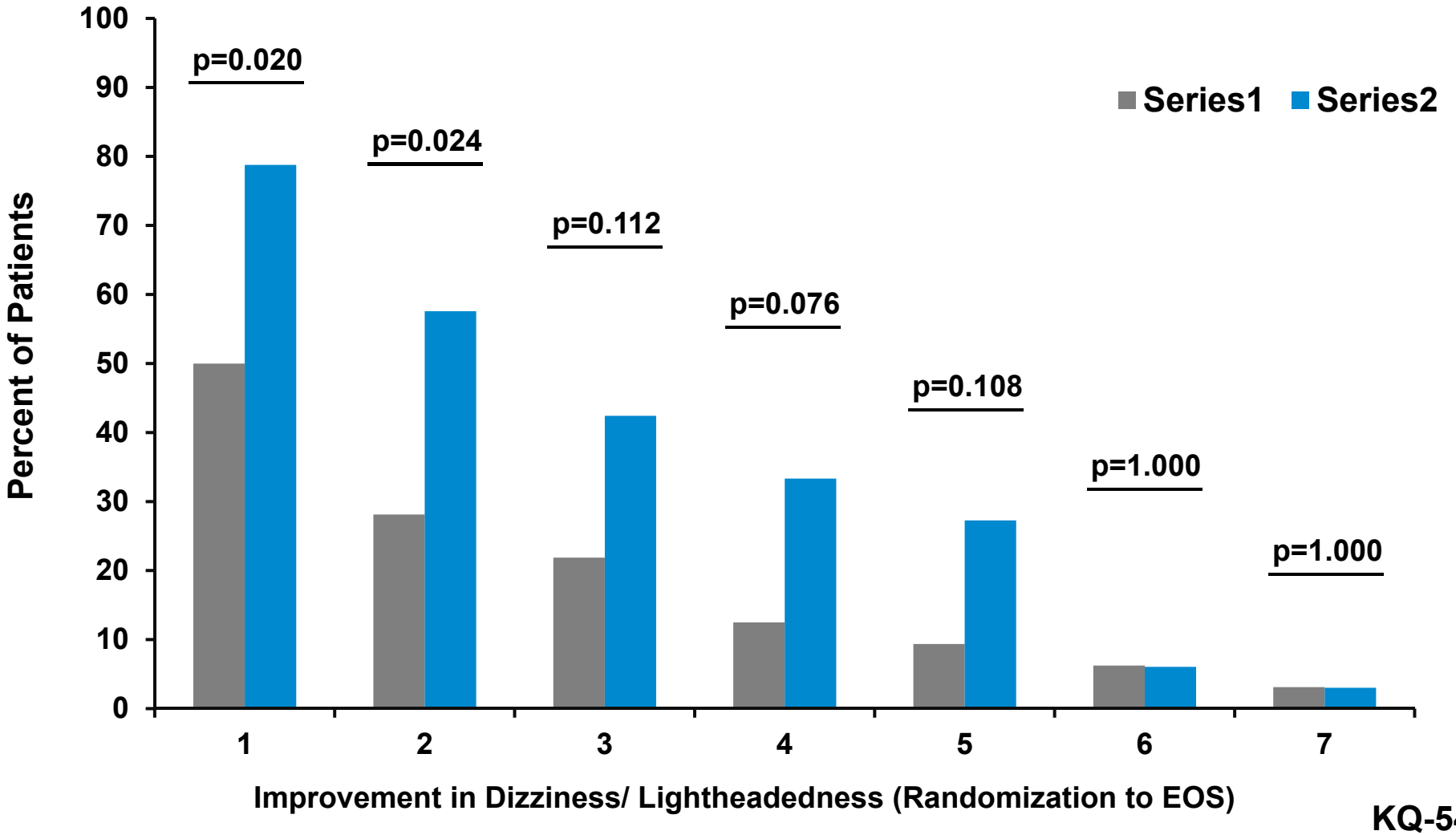
Common AEs by Fludrocortisone Use (>5 Patients): Study 306AB

	History of Fludrocortisone Use				No History of Fludrocortisone Use			
	Placebo (n=22)		Droxidopa (n=32)		Placebo (n=89)		Droxidopa (n=79)	
	n	(%)	n	(%)	n	(%)	n	(%)
Total Patients with an AE	**18**	**(81.8)**	**25**	**(78.1)**	**72**	**(80.9)**	**63**	**(79.7)**
Contusion	3	(13.6)	3	(9.4)	9	(10.1)	3	(3.8)
Excoriation	2	(9.1)	3	(9.4)	6	(6.7)	3	(3.8)
Hypertension	0	0.0	3	(9.4)	1	(1.1)	5	(6.3)
Headache	1	(4.5)	2	(6.3)	7	(7.9)	13	(16.5)
Skin laceration	2	(9.1)	2	(6.3)	8	(9.0)	3	(3.8)
Urinary tract infection	3	(13.6)	2	(6.3)	2	(2.2)	2	(2.5)
Dizziness	1	(4.5)	1	(3.1)	4	(4.5)	10	(12.7)
Fatigue	0	0.0	1	(3.1)	6	(6.7)	7	(8.9)
Blood pressure increased	1	(4.5)	1	(3.1)	6	(6.7)	3	(3.8)
Oedema peripheral	2	(9.1)	1	(3.1)	4	(4.5)	4	(5.1)
Insomnia	1	(4.5)	1	(3.1)	1	(1.1)	4	(5.1)
Balance disorder	0	0.0	1	(3.1)	3	(3.4)	2	(2.5)
Constipation	2	(9.1)	1	(3.1)	1	(1.1)	2	(2.5)
Parkinson's disease	0	0.0	1	(3.1)	2	(2.2)	3	(3.8)
Nausea	1	(4.5)	0	0.0	4	(4.5)	10	(12.7)
Diarrhoea	1	(4.5)	0	0.0	7	(7.9)	4	(5.1)
Back pain	2	(9.1)	0	0.0	5	(5.6)	2	(2.5)

Incidence of SBP >180 mmHg By Concomitant Medication Subgroups Study 306

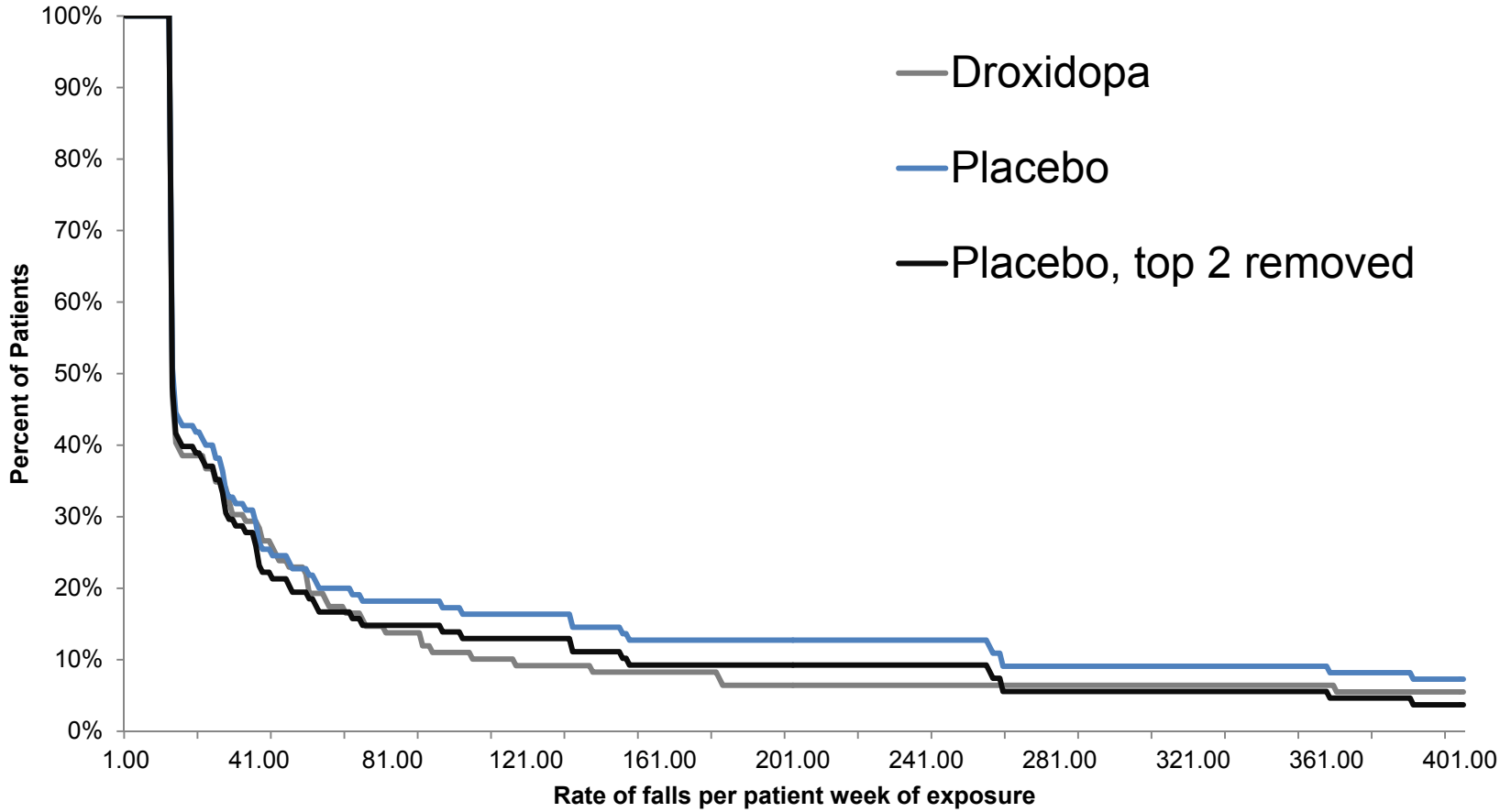
	SBP >180 mmHg at all 3 supine OST measurements			
	Baseline Visit		Any Study Visit	
	Placebo n/total (%)	Droxidopa n/total (%)	Placebo n/total (%)	Droxidopa n/total (%)
DDC-I Use				
DDC-I	2/102 (2.0)	0/98 (0.0)	2/102 (2.0)	8/98 (8.2)
No DDC-I	0/9 (0.0)	0/13 (0.0)	1/9 (11.1)	1/13 (7.7)
Fludrocortisone Use				
Fludrocortisone	2/22 (9.1)	0/32 (0.0)	1/22 (4.5)	4/32 (12.5)
No Fludrocortisone	0/89 (0.0)	0/79 (0.0)	2/89 (2.2)	5/79 (6.3)
Dopaminergic Agents				
Dopaminergic	0/36 (0.0)	0/36 (0.0)	3/75 (4.0)	6/75 (8.0)
No Dopaminergic	2/75 (2.7)	0/75 (0.0)	0/36 (0.0)	3/36 (8.3)
DEDAs				
DEDA	0/47 (0.0)	0/45 (0.0)	2/47 (4.3)	4/45 (8.9)
No DEDA	2/64 (3.1)	0/66 (0.0)	1/64 (1.6)	5/66 (7.6)

Study 301, US Sites Only:
Dizziness/Lightheadedness Response

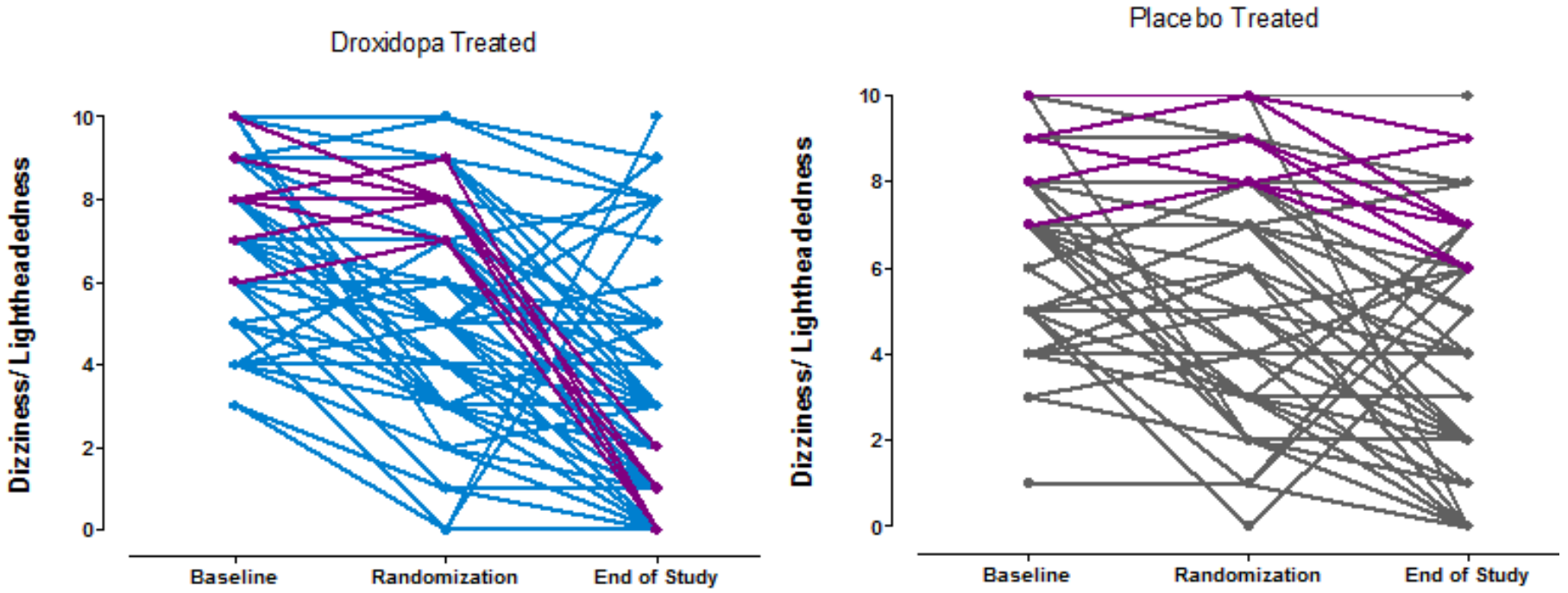


KQ-54

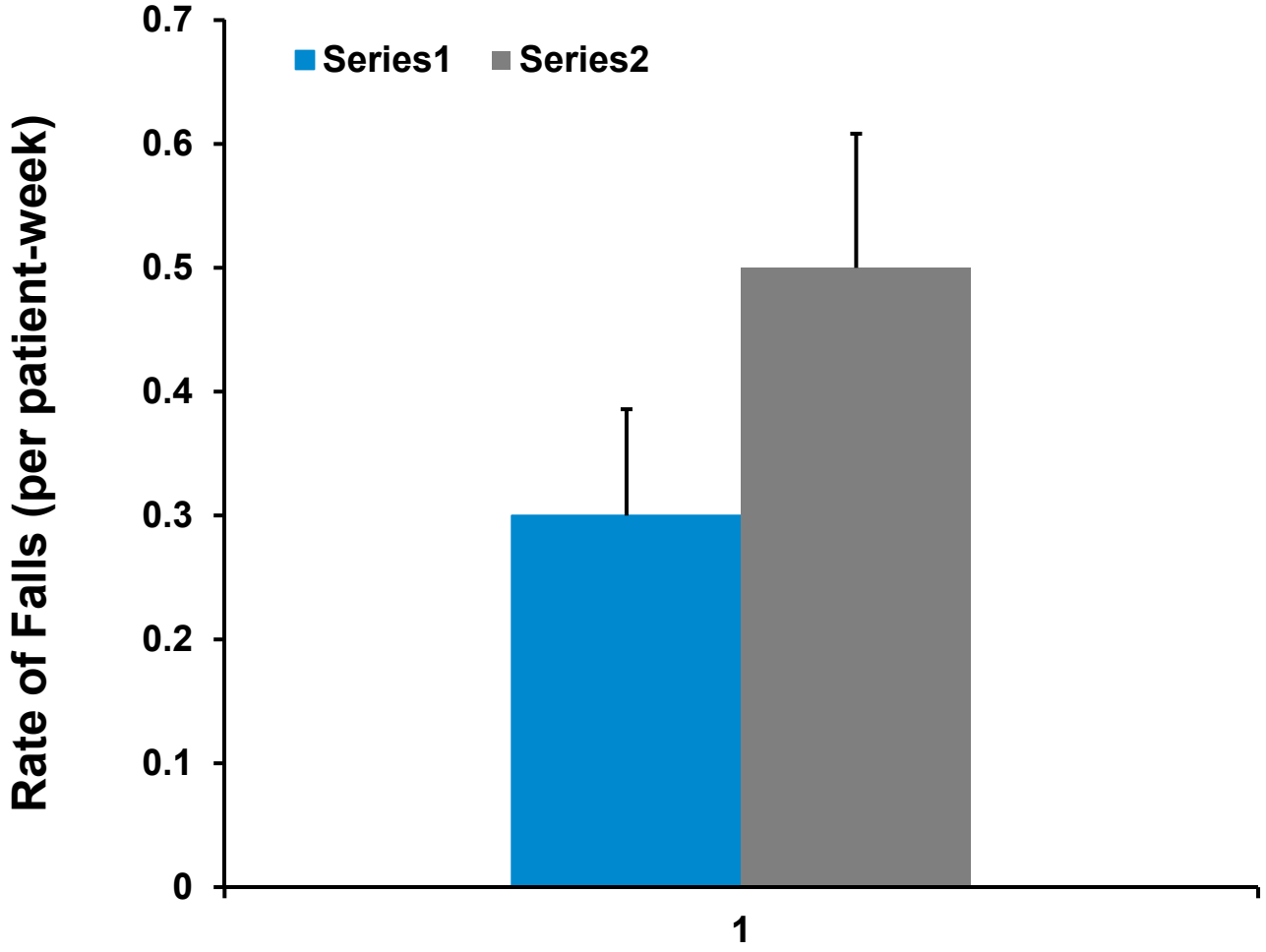
Study 306B + Interim Analysis Dataset:
Rate of Falls Per Week (ITT) – Top 2 Placebo Fallers Removed



Study 301: Dizziness by Study Visit

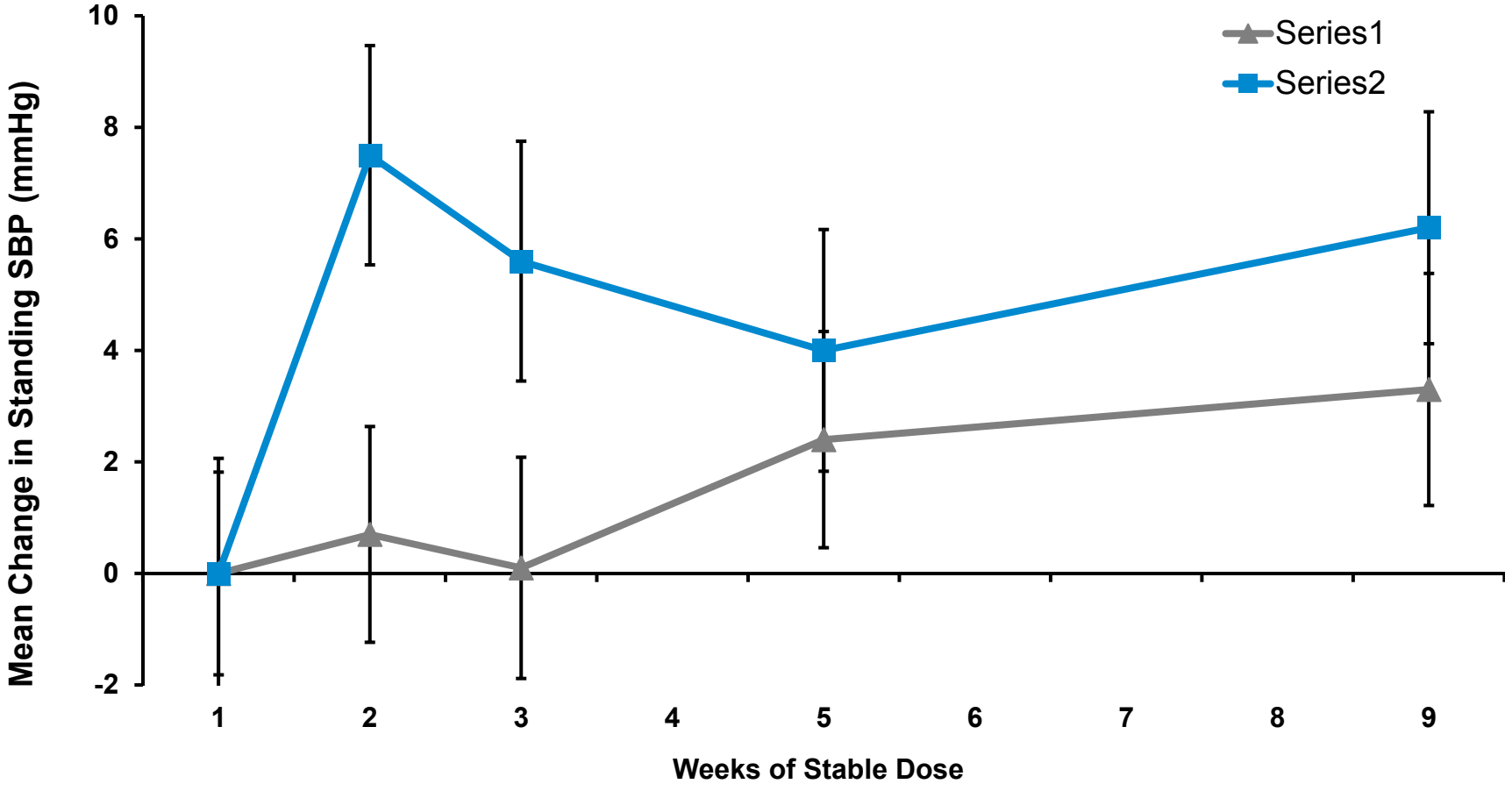


Study 306 Rate of Falls (per patient-week): Top 2 Fallers Removed



EF-401

Study 306B + Interim Analysis Dataset: Durability in Standing SBP



p-value:	**p=0.007**	**p=0.077**	**p=0.872**	**p=0.276**
Placebo:	n=105	n=102	n=98	n=92
Droxidopa:	n=90	n=91	n=86	n=84

EF-579

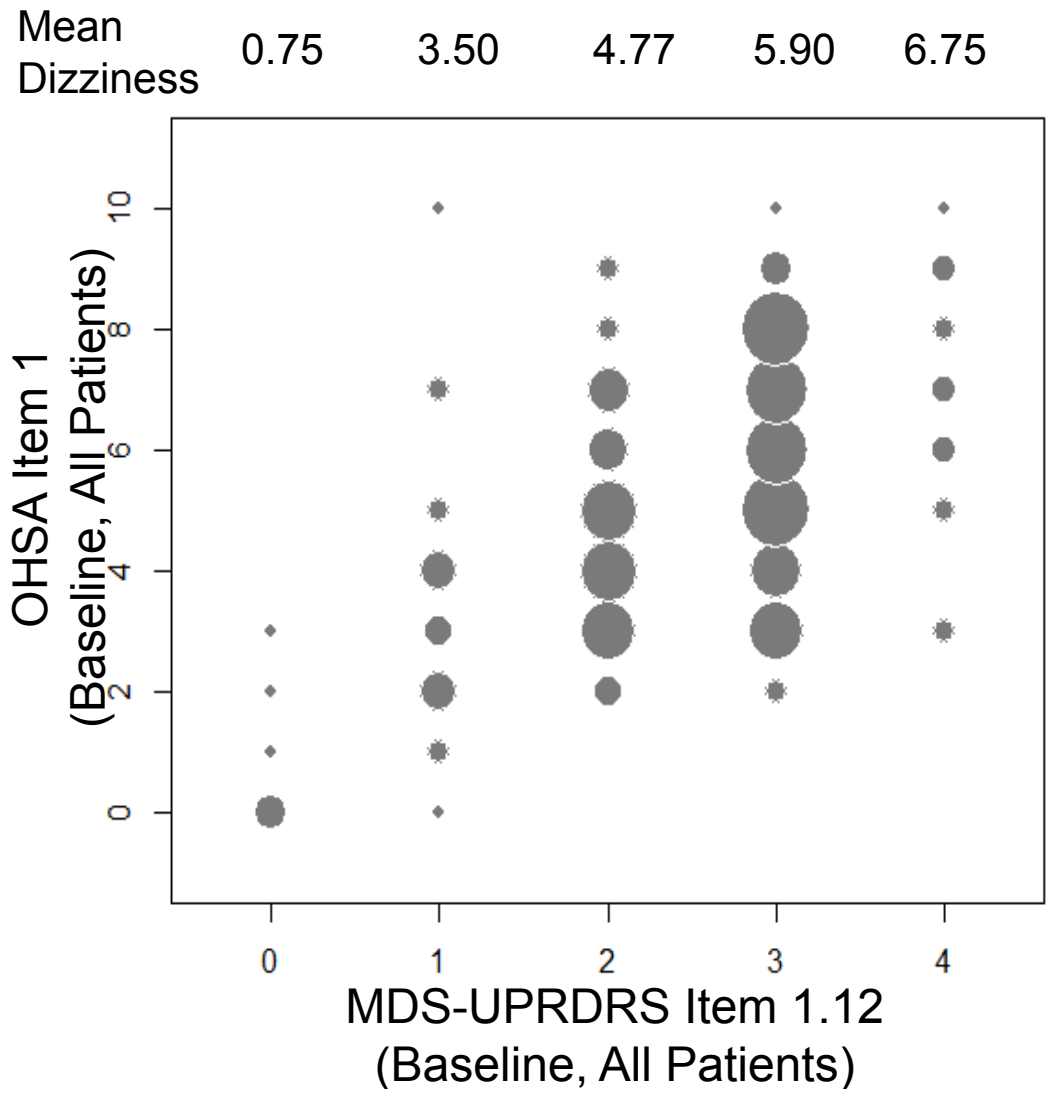
Treating OH by Increasing BP Not Appropriate for Diabetic Autonomic Neuropathy Patients

- Catecholamines, including NE, are key regulators of glucose metabolism[1] and NE directly stimulates glucose uptake, independent of insulin, in obese insulin-resistant patients[2]

[1]Exton and Park. 1968, *J Biol Chem.* 243(16): 4189-96; Meguid et al. 1975, *J. Surg. Res.* 18(4):365-9; Chu et al. 1996, *Am J Physiol.* 271(Pt. 1):E127-37

[2] Flechtner-Mors et al. 2004, *Obes. Res.* 12(4):612-20

OHSA Item 1: Study 306
Correlation to Functional Effects



MDS-UPDRS Item 1.12: "Over the past week, have you felt faint, dizzy, or foggy when you stand up after sitting or laying down?"

0: No dizzy or foggy feelings

1: Dizzy or foggy feelings occur. However they do not cause me troubles doing things

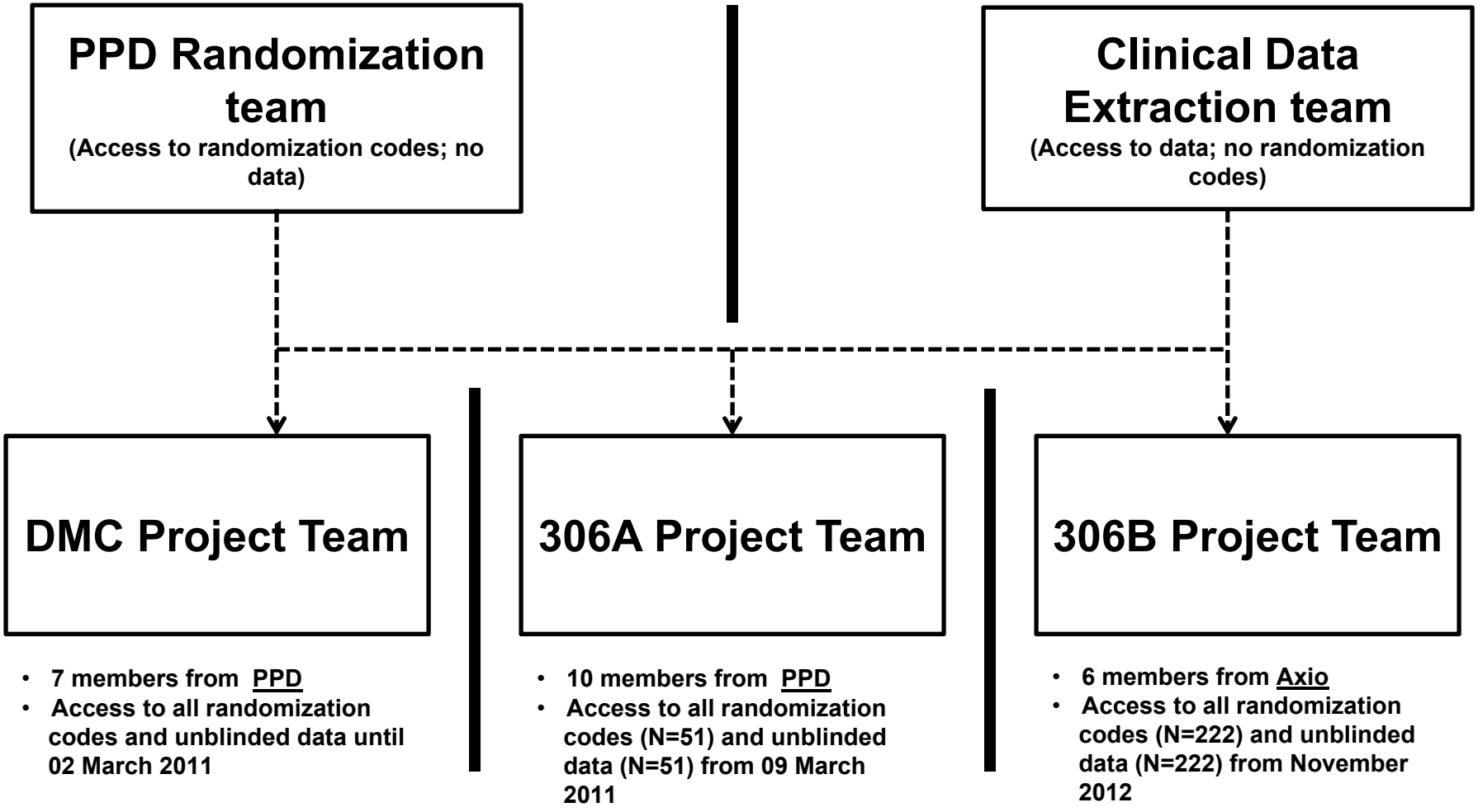
2: Dizzy or foggy feelings cause me to hold on to something, but I do not need to sit or lie back down

3: Dizzy or foggy feelings cause me to sit or lie down to avoid fainting or falling

4: Dizzy or foggy feelings cause me to fall or faint

BG-064

NOH306 Database Firewalls in Place



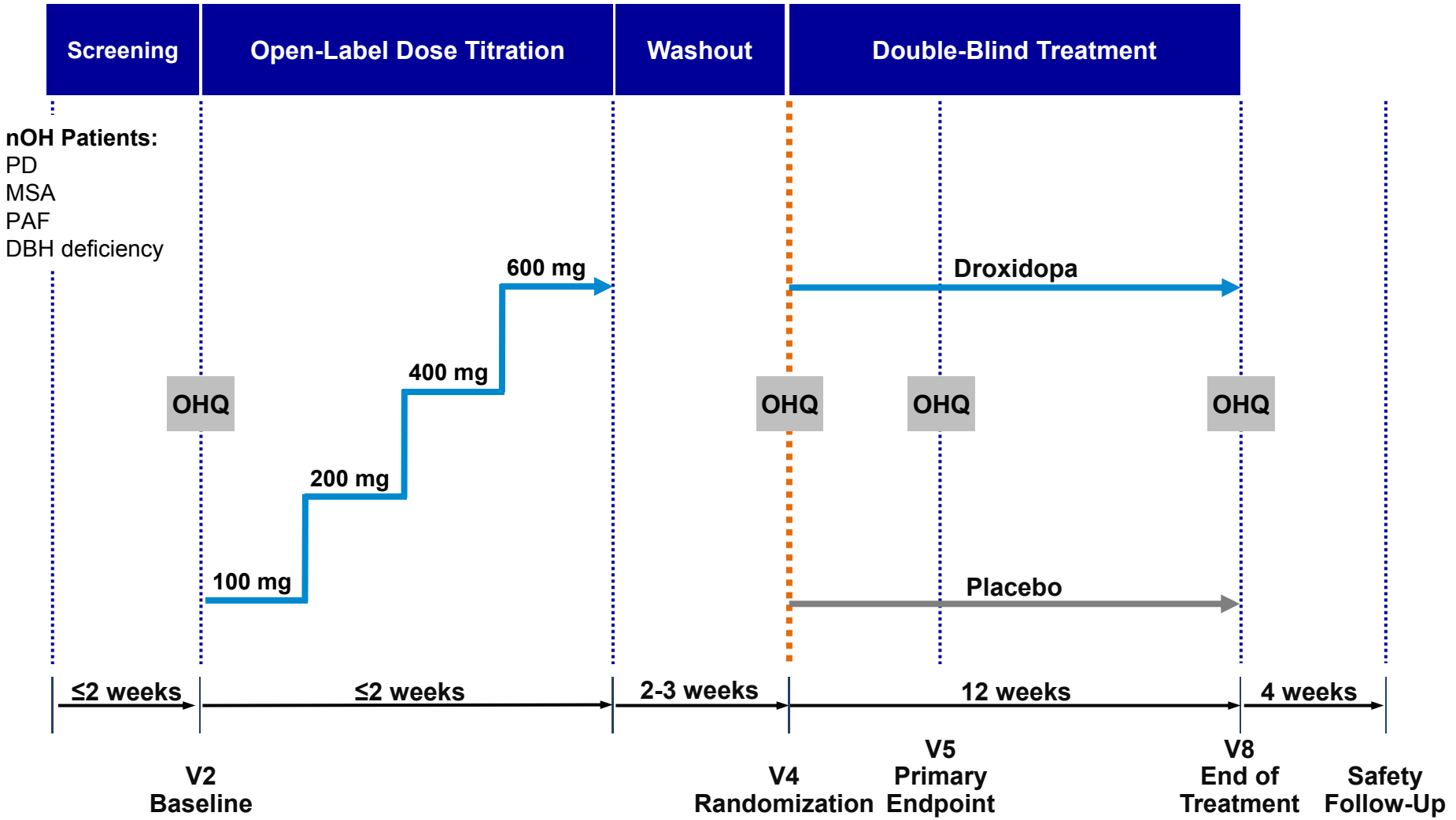
Study 306B Dropouts:
Dose & Timing

Patient	Last Dose	Days on Drug	Last Efficacy Assessment	ETV Visit
110006	Placebo	11	Baseline	No
112004	Placebo	2	Baseline	No
161005	Placebo	6	Baseline	No
160005	Placebo	5	Off Drug (1 day)	Yes
122014	Placebo	1	Off Drug (2 days)	Yes
176003	Placebo	8	Off Drug (4 days)	Yes
140001	100	1	Baseline	No
160001	100	4	Baseline	No
164005	100	14	Baseline	No
113008	100	1	Off Drug (1 day)	Yes
132004	100	4	Off Drug (7 days)	Yes
115004	200	18	On Drug (5 days)	Yes
110004	300	8	Baseline	No
184003	300	4	Off Drug (3 days)	Yes
152004	400	15	Baseline	No
142003	400	14	Off Drug (10 days)	Yes
118004	400	5	Off Drug (12 days)	Yes
156002	400	7	On Drug (4 days)	Yes
132010	600	10	On Drug (1 day)	Yes
182008	600	9	On Drug (1 day)	Yes
183002	600	12	On Drug (1 day)	Yes
183007	600	16	On Drug (2 days)	Yes
183008	600	21	On Drug (7 days)	Yes
183009	600	21	On Drug (7 days)	Yes

Response Shift:
Well-Established Confounding Factor for PRO Outcomes in Long Term Trials

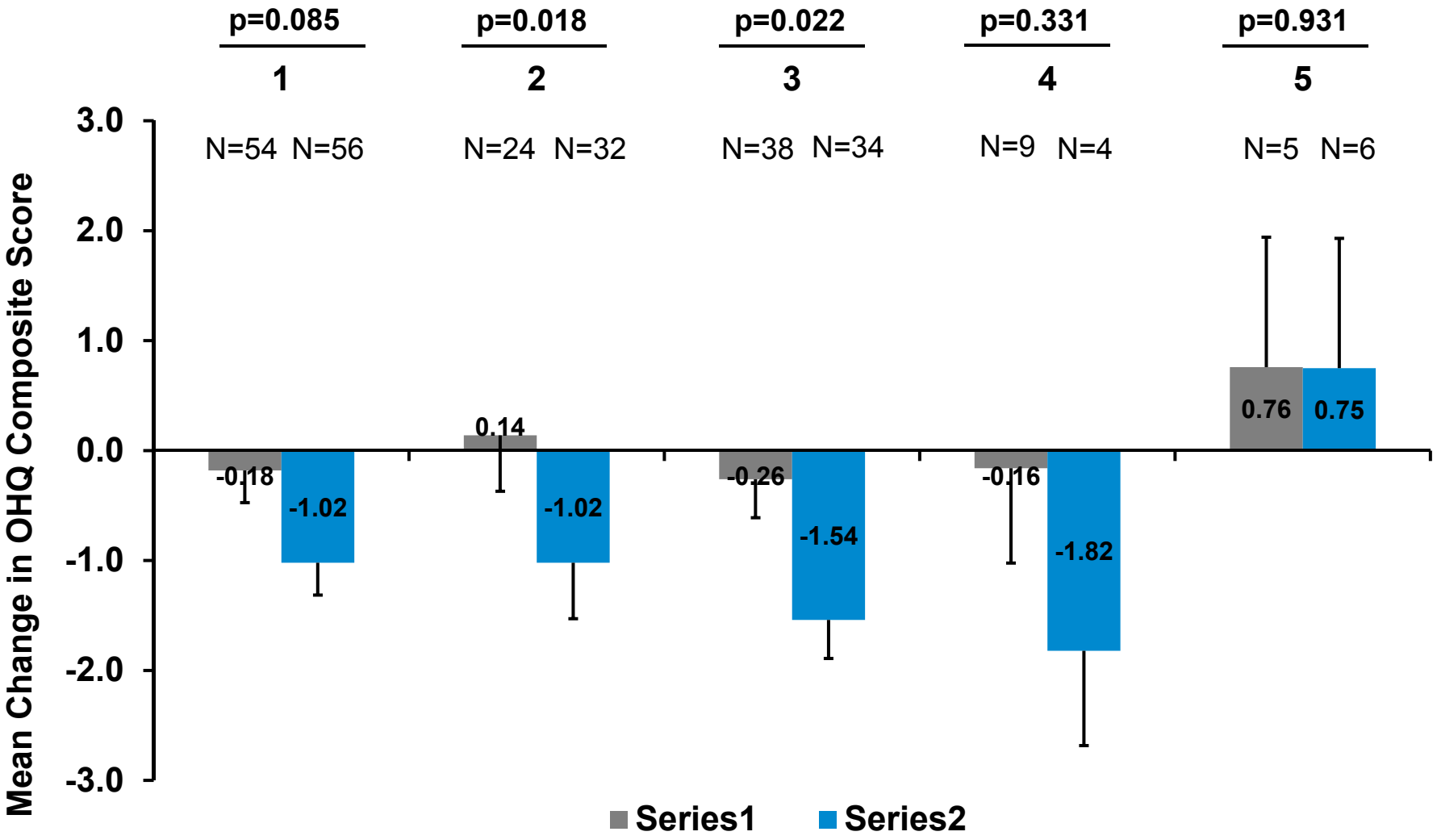
- Ring L, et al. Response shift masks the treatment impact on patient reported outcomes (PROs): the example of individual quality of life in edentulous patients. Health and Quality of Life Outcomes. 2005;3:55.
- Schwartz CE, Finkelstein JA. Understanding inconsistencies in patient-reported outcomes after spine treatment: response shift phenomena. Spine J. 2009;9(12):1039-45.
- Ahmed S, et al. Response shift influenced estimates of change in health-related quality of life poststroke. J Clin Epidemiol. 2004;57(6):561-70.
- Nagl M, Farin E. Response shift in quality of life assessment in patients with chronic back pain and chronic ischaemic heart disease. Disabil Rehabil. 2012;34(8):671-80.
- Razmjou H, Schwartz CE, Holtby R. The impact of response shift on perceived disability two years following rotator cuff surgery. J Bone Joint Surg Am. 201;92(12):2178-86.
- Barclay-Goddard R, et al. Response shift was identified over multiple occasions with a structural equation modeling framework. J Clin Epidemiol. 2009;62(11):1181-8.
- Korfage ID, de Koning HJ, Essink-Bot ML. Response shift due to diagnosis and primary treatment of localized prostate cancer: a then-test and a vignette study. Qual Life Res. 2007;16:1627-34.
- Schwartz CE. Applications of response shift theory and methods to participation measurement: a brief history of a young field. Arch Phys Med Rehabil. 2010;91(9 Suppl):S38-43.
- Rapkin BD, Schwartz CE. Toward a theoretical model of quality-of-life appraisal: Implications of findings from studies of response shift. Health and Quality of Life Outcomes. 2004;2(14):1-12.

Study 401:
Study Design



BG-209

OHQ Composite - Primary Diagnosis: CFR (Studies 301 and 302)



EF-015

AEs by Age (≥ 10 Patients with AE): Study 306B + Interim Analysis Dataset

	Placebo			Droxidopa		
	< 65 N=19	≥ 65 N=89	≥ 75 N=45	< 65 N=13	≥ 65 N=101	≥ 75 N=39
Total Patients with AE	**18 (94.7%)**	**69 (77.5%)**	**31 (68.9%)**	**9 (69.2%)**	**82 (81.2%)**	**32 (82.1%)**
Headache	5 (26.3%)	3 (3.4%)	1 (2.2%)	1 (7.7%)	14 (13.9%)	6 (15.4%)
Contusion	4 (21.1%)	8 (9.0%)	4 (8.9%)	1 (7.7%)	5 (5.0%)	2 (5.1%)
Oedema peripheral	1 (5.3%)	5 (5.6%)	5 (11.1%)	0 (0.0%)	5 (5.0%)	5 (12.8%)
Skin laceration	2 (10.5%)	8 (9.0%)	3 (6.7%)	1 (7.7%)	4 (4.0%)	2 (5.1%)
Dizziness	2 (10.5%)	3 (3.4%)	0 (0.0%)	1 (7.7%)	10 (9.9%)	4 (10.3%)
Diarrhoea	1 (5.3%)	7 (7.9%)	5 (11.1%)	1 (7.7%)	3 (3.0%)	2 (5.1%)
Excoriation	1 (5.3%)	7 (7.9%)	2 (4.4%)	0 (0.0%)	6 (5.9%)	3 (7.7%)
Fatigue	1 (5.3%)	5 (5.6%)	2 (4.4%)	0 (0.0%)	8 (7.9%)	2 (5.1%)
Blood pressure increased	1 (5.3%)	6 (6.7%)	3 (6.7%)	0 (0.0%)	4 (4.0%)	1 (2.6%)